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Foreword to Symposium on Peripheral Vascular Disorders

THE PURPOSE of this symposium is to present representative papers dealing with the aspects of the rapidly growing field of peripheral vascular physiology and disease. Included are reports of physiologic studies possessing clinical implications, descriptions of simple methods of diagnosis of arterial and venous difficulties of the extremities and discussions of the appropriate medical and surgical treatment of these conditions.

The symposium emphasizes the fact that in recent years great strides have taken place in the surgical therapeutic approach to peripheral vascular disorders. First, with the use of homologous arterial and autogenous or homologous venous grafts, and later, when these demonstrated inherent weaknesses, with various types of arterial plastic substitutes, successful attempts have been made to replace thrombosed portions of the aortic bifurcation and to bridge segmental arterial occlusions in the extremities. Thus an effective clinical means has become available for increasing local blood flow, with a corresponding reduction in the symptoms of arterial insufficiency and in the incidence of amputation of limbs. At the same time, sympathectomy has been proportionately downgraded as a therapeutic aid.

An important point that has also been brought out in the symposium is the fact that much more investigation is necessary in this field. Lacking, for example, are methods for anticipating intravascular clotting. If such were available, it is possible that the serious complication of pulmonary embolism could in most instances be prevented by adequate medical and surgical treatment. More critical evaluation of the various drugs used as therapy is likewise essential, as are comprehensive studies on the mechanisms responsible for the growth of arterial and venous collateral circulation. Focusing attention on some of the gaps in our knowledge of this field may, it is hoped, encourage the formation of experimental and clinical programs for the solution of existing problems.

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Symposium on Peripheral Vascular Disorders

Blood Flow Redistribution in the Human Extremity

The Diversion Phenomenon*

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THAT THE circulation through the various tissues composing the extremities differs morphologically and in certain functional features is well established. Nevertheless, there seems to be a widespread tendency to categorize procedures and agents as general dilators or general constrictors.[1] In the choice of a therapeutic agent for treatment of circulatory inadequacies, the specific tissue in which the deficiency is found, and the possible etiology of the diminished blood flow, must be carefully considered. Indeed, there is reason to believe that a vasodilating procedure may actually diminish rather than increase the blood flow if the dilatation is restricted to that tissue which is normal, diverting blood flow from the already deficient circulation.[2] Since the arterioles of skin and muscle show qualitative and quantitative differences in responsiveness to various procedures, diversion of blood flow is a theoretical possibility. Finally, there is some evidence that an increase in the total blood flow through a tissue is not necessarily associated with increased nutrition of the tissue since, as is well known in the case of skin, an increased total blood flow may result from the simple procedure of opening non-nutritive arteriovenous anastomoses.[3] The possibility that similar non-nutritive channels occur in skeletal muscle has been seriously considered and some evidence which tends to establish this point is now being accumulated.[4]

In this paper we will present some examples of the actual diversion of blood among the several possible circulations.

CLINICAL EXAMPLES

DIVERSION THROUGH MUSCLE AT EXPENSE OF SKIN

As an illustration of increased blood flow through muscle at the expense of flow through skin, we are presenting data on two subjects. In the normal subject, there is a slight and transient decrease in blood flow through the toe immediately after the cessation of exercise (Fig. 1A). In the patient with arteriosclerosis obliterans, there is no measurable blood flow through the toe during the first minute or two after cessation of exercise (Fig. 1B); neither posterior tibial nerve block nor sympathectomy is able to reverse this change (Figs. 1C and 1D). In a previous study[2] we showed that, at the same time that the blood flow through the toe reaches these minimal values, blood flow through the calf muscles of that leg is vastly increased. This seems to be clear-cut evidence

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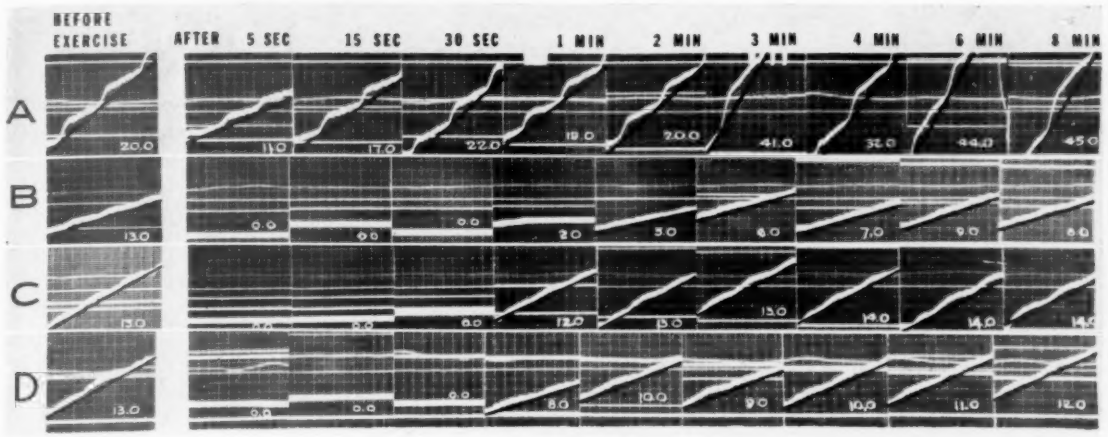

FIG. 1. Plethysmographic tracings of venous occlusion blood flow measurements in the toe of a normal subject (A) and in a patient with arteriosclerosis obliterans without treatment (B), after posterior tibial nerve block (C), and after sympathectomy (D). Blood flow measurements were made before and at indicated intervals after exercise of the calf muscles. The records were corrected to read in cu.mm./4 cc. of digit/second.

for the redistribution of blood through the muscle at the expense of the blood flow through the toe in a patient with a restricted arterial inflow.

DIVERSION BETWEEN SKIN AREAS

Shunting of flow through the skin from the proximal to the more distal portions of the limb is illustrated in a fifty-seven year old man who had advanced arteriosclerosis obliterans of the lower extremities. Prior to sympathectomy, the skin of the foot and toes was somewhat atrophic and the toes were cool. After surgery, there was an immediate rise in the temperature of the skin of the toes, reflecting release of sympathetic tone in skin of the distal part of the foot. However, by the third postoperative day, a gangrenous area appeared over the dorsal and more proximal portions of the foot in the region of the dorsalis pedis artery. The diversion here may have been caused by greater dilatation of the distal than of the proximal vessels of the skin of the foot, since sympathetic vasomotor tone is greater in the former than in the latter. Similar cases have been described by Freeman and his associates.[5]

DIVERSION FROM DISEASED TISSUES TO DILATED NORMAL TISSUES

Diversion of blood flow to normal vascular beds from an obstructed vascular bed is illustrated in a twenty-seven year old man who had thrombosis of the left axillary artery as a result of a gunshot wound. Heat applied to the body resulted in an increase in pulsations and blood flow through the right index finger

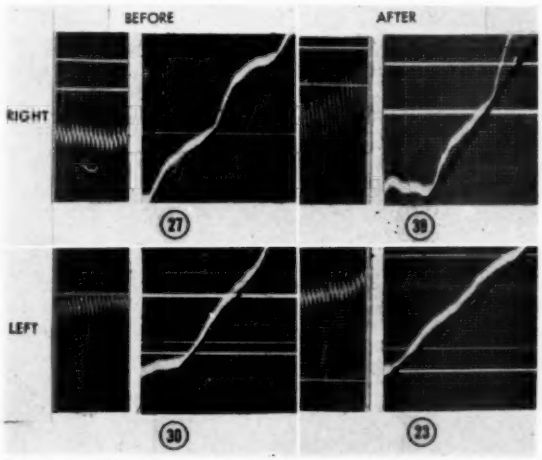

FIG. 2. Simultaneous plethysmographic tracings of pulse volume and venous occlusion blood flow measurements in finger tips of the right and left hands of a patient with limited blood flow into the left arm due to thrombosis of left axillary artery. Measurements were made before and after body heating to induce vasodilatation. Note the increase in both pulse amplitude and blood flow in the normal (right) finger, and the simultaneous decrease in these parameters in the restricted (left) finger. Numbers in circles are calculated blood flows in cu. mm./4 cc. of digit/second.

with a simultaneous decrease in these measurements in the left index finger (Fig. 2). Another example is seen in Figure 3 which shows a plethysmogram from a thirty-five year old white man with typical thromboangiitis obliterans of the vessels of the right foot but with a normal left leg and foot. Ten milligrams of isoxsuprine (Mead 5029)* were given intra-

* Mead Johnson Company, Evansville, Indiana.

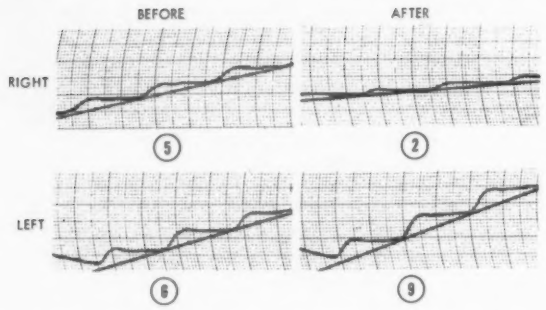

FIG. 3. Digital flow in diseased right toe with simultaneous flow in normal toe of the left foot before and after the administration of isoxsuprine (Mead 5029). The flow decreased on the diseased side and increased on the normal side. Flow is measured in cu. mm./4 cc. of digit/second (numbers in circles).

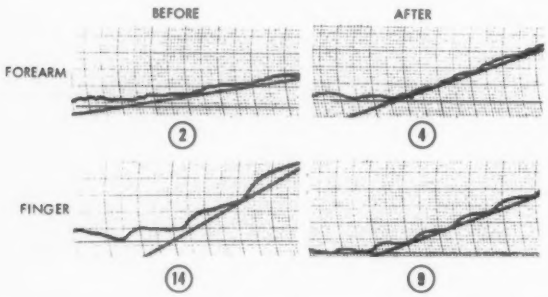

FIG. 4. Simultaneous measurements of blood flow through forearm and digit before and after the intravenous injection of norsuprifen (Arlidin). The muscle flow increased with a simultaneous decrease in skin flow. Forearm flow is measured in cc./100 cc./minute and finger flow in cu. mm./4 cc./second (numbers in circles).

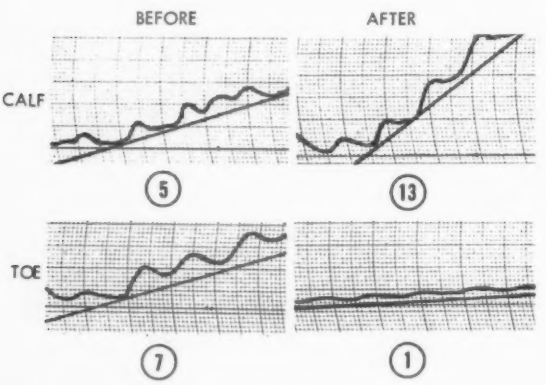

FIG. 5. Plethysmograms of right calf and toe of patient with thrombophlebitis recorded almost simultaneously before and ten minutes after injection of 10 mg. isoxsuprine (Mead 5029) into the right femoral artery. Note increase in blood flow in calf and decrease in blood flow in toe after injection.

venously after which the blood flow fell in the diseased side and increased on the normal side.

Both of these results are consistent with the statement of Mendlowitz[6] and others that generalized vasodilating procedures or drugs may decrease the circulation in an extremity with obstructive arterial disease. In these cases the healthy vessels dilate, thus theoretically decreasing the pressure available for perfusing the diseased limb.

DIVERSION RESULTING FROM DRUG ACTION

When a drug has differential effects on the vasculature of muscle and of skin, an increase in the blood flow in one area may be accompanied by a simultaneous decrease in the other. One illustration of such action is shown in Figure 4; simultaneous measurements of blood flow through the forearm and finger tip were made before and fifteen minutes after the intravenous administration of 5.0 mg. of norsuprifen (Arlidin®†). The increase in forearm blood flow, essentially muscle flow, with a slight decrease in finger tip flow, is clearly illustrated.

Another example of diversion of blood away from skin to muscle by a drug was observed in a seventy-two year old man with thrombophlebitis, in whom an intra-arterial injection of isoxsuprine (Mead 5029) was made (Fig. 5). As a result, blood flow in the calf muscle increased from 5 to 13 cc./100 cc. of leg/minute, but in the toe it decreased from 7 to 1 cu. mm./4 cc. of toe/second. The toe, which previous to injection, appeared essentially normal, became pale, mottled and cyanotic. This condition lasted for approximately thirty minutes, after which circulation in the toe increased and circulation in the calf decreased.

Whether these decreases in skin flow are the result of a simple diversion through muscle or whether they are in part due to a direct action of the drugs on the blood vessels in the skin is not clear from the data available. However, there is certainly the possibility that the decrease in skin flow is a reflection of a diversion of blood to the muscle circulation.

The converse diversion of flow from calf muscle to skin of the toe has been observed with other drugs employed in our laboratory, notably the DH ergot alkaloids (Hydergine®‡).

† U. S. Vitamin Company, New York, New York.
‡ Sandoz Pharmaceuticals, Hanover, New Jersey.

Comments

A precise regulation of the redistribution of the blood volume among the several tissues of the body was proposed by DeBakey et al.[7] and named hemometakinesia. Continuous measurements of the blood volume contained in parts of the extremities showed that local increases were often accompanied by simultaneous and perhaps compensatory decreases elsewhere. This hemometakinesia serves to conserve total blood volume. The volume of blood contained in a tissue, however, cannot be used as a measure of the blood flow through that tissue. We are suggesting a diversion of flow, in contrast to volume of blood contained, as a consequence of limited regional blood supply.

Compensatory flow relationships may result from the active intervention of reciprocal vasomotor responses through reflex systems.[8] However, in certain circumstances, the hemodynamics of a particular system would redistribute the flow between two sets of blood vessels on a purely physical basis. Where the maximum blood flow through an extremity is limited by the capacity of the arterial input, dilatation of any distal vascular bed would result in a drop in pressure within the arterial segment and a consequent decrease in blood flow through the collateral vascular networks which have not altered their resistance. This system is analogous to a house lighting circuit with inadequate main supply lines; the introduction of a sudden load, e.g., turning up an electric heater, would result in diminishing the electrical flow through the several circuits and hence a dimming of the lights would occur.

Theoretically, such dynamic diversions of blood flow between vascular beds may occur under a large variety of conditions. Several of these circumstances have been indicated in Table I. However, not all of these conditions have been demonstrated as yet, and indeed, some of them may be improbable.

An actual example of such hemodynamic diversion is the large increase in blood flow through an exercising muscle of a limb with partially occluded arterial input, accompanied by a dramatic fall in the blood flow through the skin of that same limb, as illustrated in Figure 1. This type of diversion requires that the maximum flow through the arterial system be insufficient to supply simultaneously the maximum demands of the several tissues. Apparently such a situation is rarely encountered in the normal, healthy individual but can be demonstrated when significant arterial disease is present.

TABLE I

Conditions Under Which the Diversion Phenomenon May Occur

Diversion of Flow	Reflex Heating	Sympathectomy	Drug Action	Exercise
Skin to muscle	−	−	+*	+
Muscle to skin	±	+	+†	−
Proximal to distal (skin)	+	+	?	−
Distal to proximal (skin)	±‡	−	?	−
Nutritive to shunt (skin or muscle)	±	+	?	−
Shunt to nutritive (muscle)	−	−	?	+
Disease to healthy tissue	+	+	+§	±

Note: + indicates a diversion which has been demonstrated; ± indicates theoretically possible diversion of which no direct demonstration is presented; − indicates situations in which diversion is theoretically impossible or unlikely; ? indicates situations in which no drug known to us could induce the diversion.

* Diversion of flow from skin to muscle can be demonstrated after the administration of norsuprifen (Arlidin) or isoxsuprine (Mead 5029). In both cases the diversion from skin to muscle could be purely mechanical, or a direct constrictor effect of the drug on the arterioles of the skin could be present.

† Diversion of flow from muscle to skin follows the administration of the DH ergot alkaloids (Hydergine). Again the diversion could be purely mechanical but the possibility of direct constrictor effects of these compounds on the blood vessels of skeletal muscle must be considered.

‡ Such diversion would occur only under the following special circumstances: If due to disease the vasoconstrictor sympathetic outflow to the upper extremity had been lost, while the cholinergic vasodilator sympathetic outflow to the skin of the proximal part of the extremity remained intact, reflex vasodilatation would theoretically increase blood flow through this proximal segment, at the expense of the denervated distal portion.

§ Any systemic vasodilator would serve to increase blood flow through the normally responding tissues of the body, while the flow through the diseased area with a fixed arteriolar caliber would tend to diminish.

Regional Differences in Arteriolar Responses: Physiologic studies indicate distinct differences in the responsiveness of the blood vessels in different parts of the skin; the arterioles of the distal portions of the extremities are apparently under a high degree of tonic sympathetic vasoconstrictor influence, whereas those of the skin of the more proximal portions have little or no vasoconstrictor tone. Conversely, active vasodilator fibers exercise a profound influence on the blood flow through the skin of the forearm, but have little or no vascular effect in the fingers.[9,10] Thus, it is theoretically possible to divert blood flow from skin of the calf to the skin of the toes or vice versa if the inflow conditions are limited and if the method chosen for dilatation is based on one of these mechanisms with specific regional influence. Paradoxical gangrene after sympathectomy, as Freeman pointed out, is probably related to such diversion.[5]

Similar redistribution of flow may occur between normal and diseased vascular beds. The fixed resistance of the diseased vessels would permit a lesser perfusion through the tissue when normal vessels dilate to divert the limited inflow (Fig. 2). This situation may result in the diversion of flow between localized regions of any particular tissue when dilator procedures are applied.

Certain drugs and hormones exercise differential influences on the vasculature in different tissues. Intravenous administration of epinephrine constricts the vasculature of the skin, but has a profound dilator effect on skeletal muscle circulation.[11] Arlidin, according to recent studies,[12] has a similar cutaneous constrictor and muscle dilator effect. Use of these agents to induce dilatation in the face of limited inflow would seem to offer theoretical advantages in the treatment of inadequacies of muscle blood flow, but obviously, they would be contraindicated in the treatment of cutaneous ischemia or when both skin and muscle are deficient in flow.

On a microscale, diversion of blood may occur between two types of blood vessels rather than between two tissues. In the case of the skin, both the arteriovenous anastomoses and the regular capillary beds are supplied from the same system of small arteries. Here, a diversion between the nutritional vascular bed and the bypass anastomotic system has been demonstrated by Barany.[13] His studies show that sympathectomy increases the total blood flow through the skin of a patient with diabetes but simultaneously significantly decreases the nutritional flow through the skin. Although there is some dilatation of the vessels with limited flow, this is not sufficient to satisfy the demands of the widely dilated shunts.

These examples would suggest great caution in the interpretation of blood flow measurements. The readings must be obtained directly from the affected area or tissue, since it cannot be assumed that the results would parallel perfusion rates measured elsewhere. Blood flow in the toe, an area which is predominantly skin, might show an increase although muscle flow decreases. Measurement of total blood flow in a tissue—even the proper tissue—may still give information which is difficult to interpret since, as Barany[13] has pointed out, sympathectomy in the patient with diabetes may increase total blood flow but actually diminish cutaneous nutrition.

Although in the present paper we are merely calling attention to the most simple (mechanical) form of diversion, namely, that which results from a limited arterial inflow, it is entirely possible that reflex systems are available to accomplish similar diversion of blood flow between organs and that these may have disturbing effects on therapeutic procedures.

Summary

Because of the limitation of the maximum total blood flow through a diseased artery, dilatation of a distal vascular bed may cause a diversion of blood away from other tissues in that extremity where the resistance to flow is fixed. Such diversions may occur (1) when a dilating procedure acts exclusively on a single tissue in the extremity, (2) when the circulation in a given tissue is unable to respond to the agent because of disease or (3) when dilatation is limited to a single type of blood vessel in the peripheral vascular bed (the arteriovenous anastomoses). These diversions of blood flow are distinct from the "lending-borrowing" phenomenon which deals with redistribution of blood volume rather than of flow.

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Pulse Registration as a Means of Evaluating Peripheral Vascular Patency and Vasomotor Activity*

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THE REGISTRATION of the volume pulses from various parts of a limb has been found to be an accurate and simple method of demonstrating local vascular patency and changes in blood vessel tonus. The method has the following advantages over others previously employed, particularly the measurement of skin temperature: (1) The sensing pneumatic cuff of the device embraces the total cross section of the limb at each level examined, so that the resultant pulse trace reflects changes in the deep as well as the superficial arteries. (2) The cuffs are easily applied to any level of the limb, from a digit upward, avoiding examination of the digits alone, where tonus is subject to great spontaneous variations, and allowing also an appraisal of the circulation over the entire limb. (3) With this method, the reactivity of the part may be tested by direct heating or cooling. Such a direct application of thermal changes is more efficient than indirect methods in inducing changes in tone, and more nearly approximates the environmental stresses from which the symptoms of some patients arise.

The method has been used in differentiating functional from organic disease, as well as in evaluating the degree of spasm or the flexibility of the arterial system when permanent structural changes are present. The study has reinforced the concept that vascular tonus is the sum of all constrictive and vasodilatory influences. We have further been impressed by the universality of the vasoconstrictive response to cold as an expression of both functional and organic arterial disease.

METHOD

Pulse Registration and Quantitation: This aspect of the method has been detailed in a former publication,[1] but it may be summarized here. The apparatus consists of a series of pneumatic cuffs, two of which may be connected simultaneously to the transducing unit (the Infraton Pulse Oscillograph†). A pressure of 30 mm. Hg is used in the pneumatic system. The transducing element is a differential capacitor, the output of which is fed into a direct writing Sanborn recorder. A paper speed of 25 mm. per second is used throughout.

While simple inspection of the curves allows a good estimate of change in pulse configuration and an approximation of amplitude and slope, a quantitative evaluation of these two factors is available. This is made possible by calibration of the height of pulse deflection for each cuff application through a device that displaces a known volume of air in the pneumatic system. The degree of displacement of the recording pen is noted. With this calibration, the pulse trace can be expressed in two parameters. The first is mean pulse deflection (mean change in volume in cubic millimeters during one pulse cycle), noted as D in the illustrations. In arriving at this value the area under a pulse trace is measured by a planimeter. In this way the difference between a sustained and an acuminate pulse is taken into account. The second parameter is the systolic slope (rate of systolic increase in volume of the pulse in cubic millimeters per second), noted as SS in the figures. The fractions shown in some of the figures denote the attenuation of the recording used for the particular pulse trace reproduced.

Induction of Vasodilatation and Vasoconstriction: Patients were examined after resting from ten to thirty minutes in a room in which the temperature was kept

† Obtained from Medical Electronics Development Co., Long Island, New York.

* From the Department of Surgery, Peter Bent Brigham Hospital, and the Department of Anatomy, Harvard Medical School, Boston, Massachusetts.

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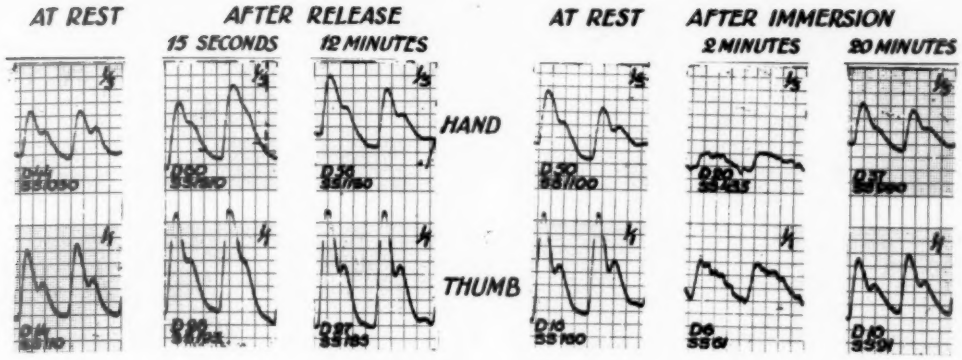

FIG. 1. *Left, reactive hyperemia* and *right, cold reaction tests* in a normal subject. The fraction at each pulse trace indicates the attenuation of the recording. D is mean pulse reflection, SS, the systolic slope. The reactions shown are average in degree.

within comfortable limits by heating in the winter and air conditioning in summer. During cold weather, undue exposure was avoided. A survey of the pulses in the resting state preceded any maneuvers aimed at testing the flexibility of vascular tone.

Vasodilatation in the hand or foot was tested by inducing a reactive hyperemia through the application of a blood pressure cuff to the wrist or ankle, inflated well above systolic level for three minutes. The pulses were registered from the foot and a toe, or the hand and a finger. It was found that there was no advantage in a more proximal application of the constricting cuff, in either the normal or diseased subjects. A longer duration of ischemia prolonged the reaction but did not increase the amplitude of response.

Vasoconstriction was induced by immersing the part to be tested in water, at a temperature of 12°C., for three minutes. The resultant constriction in pulse was as great as it would have been by a more prolonged or colder immersion. In several instances the effect of vasoconstricting and vasodilating drugs was tried in both normal and abnormal subjects.

RESULTS

NORMAL REACTION TO THE TESTS

Reactive Hyperemia: Normally reactive hyperemia is manifest and maximal in the very first reading after release of the occluding cuff (Fig. 1). The pulse shows a marked increase in systolic slope and amplitude. It is much more sustained than in the resting state; this, as well as the heightened altitude, augments the value for mean pulse deflection. The reaction is somewhat variable in the rate of its disappearance. It is usually over in a few minutes; in some subjects the pulse may quickly decline from its peak, but remains above resting levels for thirty minutes or more. These prolonged

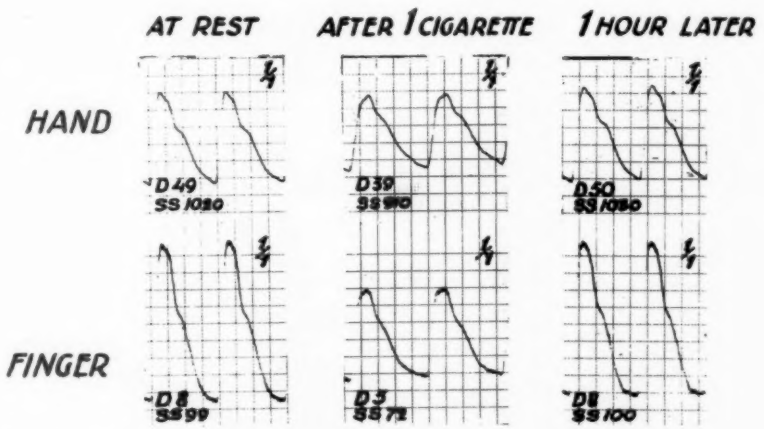

FIG. 2. *Sensitivity to tobacco.* Reaction to smoking in a young man quite sensitive to tobacco. Pulse changes in the more proximal parts of the limb were similar to those shown, indicating some central effect.

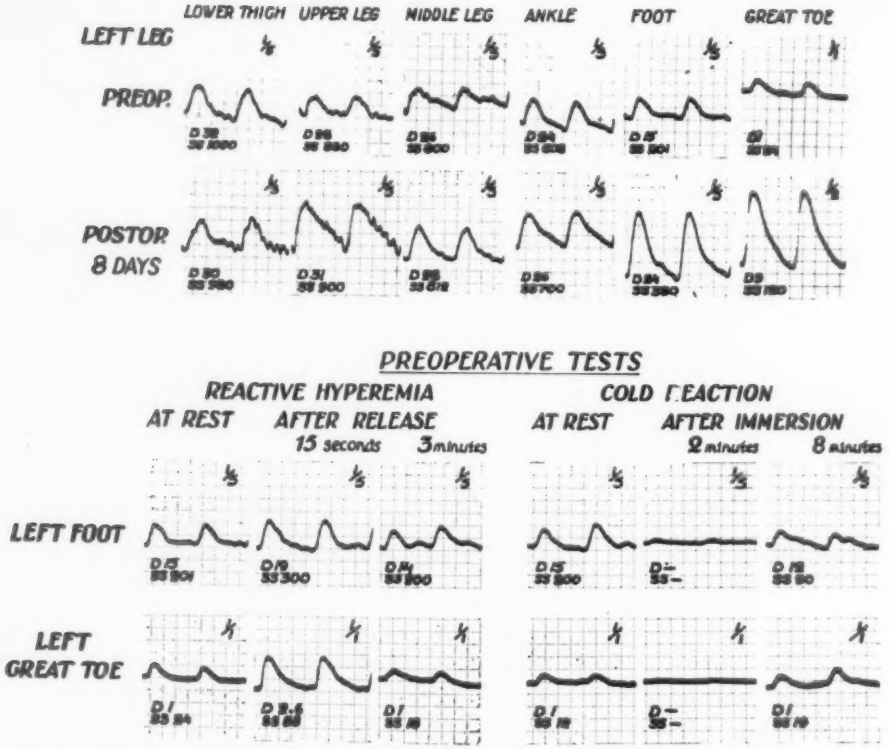

FIG. 3. *Poliomyelitis vasoconstriction.* Changes in a twenty-four-year old girl, fifteen years after poliomyelitis. *Bottom*, the preoperative tests show excellent reactive hyperemia, with extreme but transient constriction after cold immersion. *Above:* A survey of the pulses before and after lumbar sympathectomy. Postoperative vasodilation is prominent in the toe and foot, uncertain at the ankle.

responses usually mean that an exaggerated state of constriction had existed in the resting state.

The absolute level of response was greater if the part was warmed before testing, in accord with the experience of Pickering[2] (who used skin color as a measure of reactive hyperemia). The proportion of change, at least in the normal subject, from the resting to the hyperemic state, is, however, about the same whether the test is begun with the part vasoconstricted or dilated.

Reaction to Cold: The normal reaction to cold is one of vasoconstriction, with a return usually within ten minutes to the resting level or one only moderately lower. There is, however, great variation in both intensity and duration of the reaction. The constriction indeed may be extreme, especially if other vasoconstrictive influences, such as the fasting state, are at work. The wide range of response justifies the view that sensitivity to cold is an exaggeration of a normal reaction. If the pulse disappears after the cold immersion, the sensitivity must be termed abnormal, since it may give rise to pathologic consequences.

Cigarette Smoking: Sensitivity of normal subjects to cigarette smoking varied almost as much as sensitivity to the cold immersion. Figure 2 shows an example of a rather severe reaction. The effect is noticeably less marked than that of cold.

DISEASES PREDOMINANTLY VASOSPASTIC

The available pathologic studies of so-called vasospastic disease indicate that in reality organic lesions of variable extent usually exist in these states. This is particularly true of advanced Raynaud's disease (Fig. 4). Reflex sympathetic dystrophy and the vasoconstriction following poliomyelitis (Fig. 3) constitute examples of somewhat purer constrictive disease.

Poliomyelitis Vasoconstriction: While the limb after poliomyelitis may be cold to high proximal levels, this must be due to a cutaneous vasoconstriction, for the pulses are of adequate size

proximally, as above the ankle in Figure 3. The pulses of the foot and toe are small. The reaction to cold immersion is extreme, with obliteration of the pulse; but there is rapid recovery. The dilatation response is excellent both in the reactive hyperemia test and after sympathectomy, indicating the absence of organic disease.

Raynaud's Disease: Patients with Raynaud's disease may exhibit considerable vasoconstriction at room temperature as well as the characteristic episodic response to exposure to cold (Figs. 5 and 6). Their severe sensitivity to cold is shown by the disappearance of the acral pulses after cold immersion, as well as by the long time required for recovery, which may extend to twenty minutes or more. The patient shown in Figure 5 maintained considerable vasoconstriction between the episodic attacks. This limited the level of reactive hyperemia, although the relative change from the resting level was greater than the test gave after sympathectomy, when a large pulse was present in the resting state. Figure 6 shows that preoperatively vasoconstriction extended to the wrist, and that operation substantially increased the pulses to this level. The postoperative cold immersion test shows that the hand remained sensitive to cold but

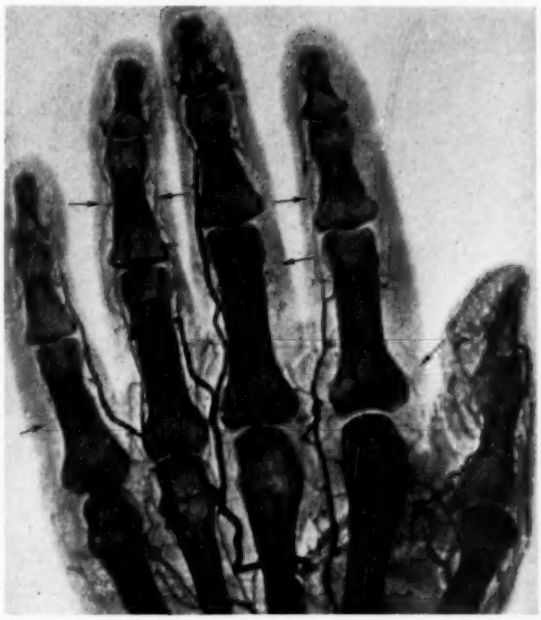

FIG. 4. *Raynaud's disease.* Arteriogram in a patient with advanced Raynaud's disease. (Courtesy of Prof. E. Malan.) Injection of 20 cc. of 70 per cent periodil was made into the brachial artery under general anesthesia. A seriographic technic was used. The figure is part of a long film exposed at eight seconds after starting the injection. The arrows point to obstructions in the digital arteries. The complete examination showed the palmar arches and the radial and ulnar arteries to be normal.

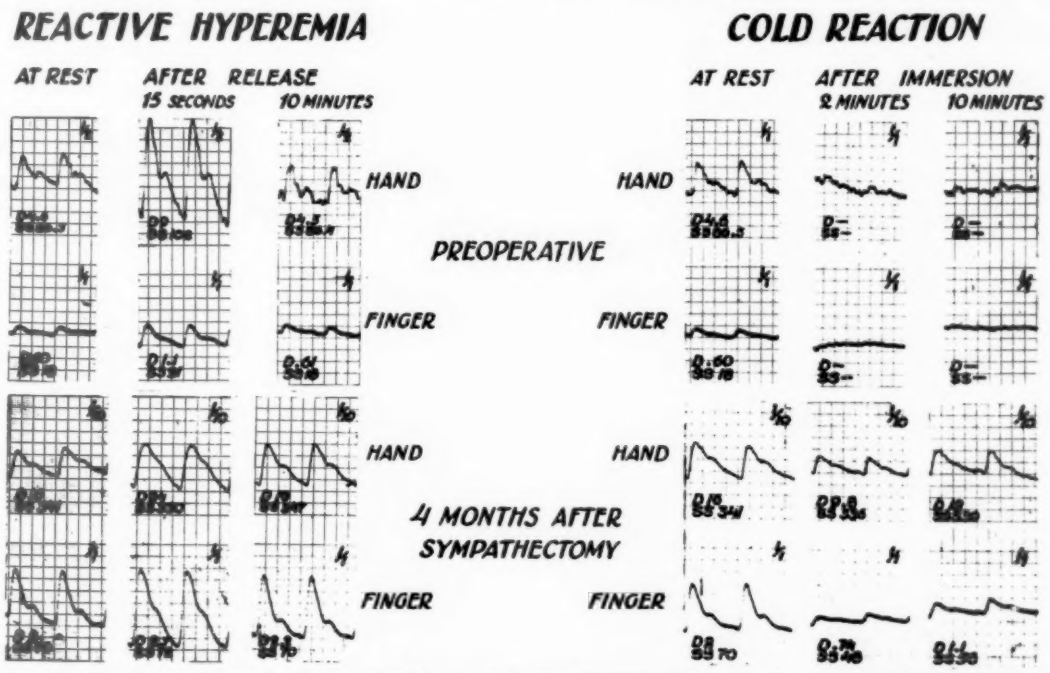

FIG. 5. *Reactions in Raynaud's disease.* Cold immersion after sympathectomy produced a constriction about as great, proportionate to the resting pulse level, as that shown before operation. However, postoperatively, the pulse is not obliterated, and the reaction is not as prolonged.

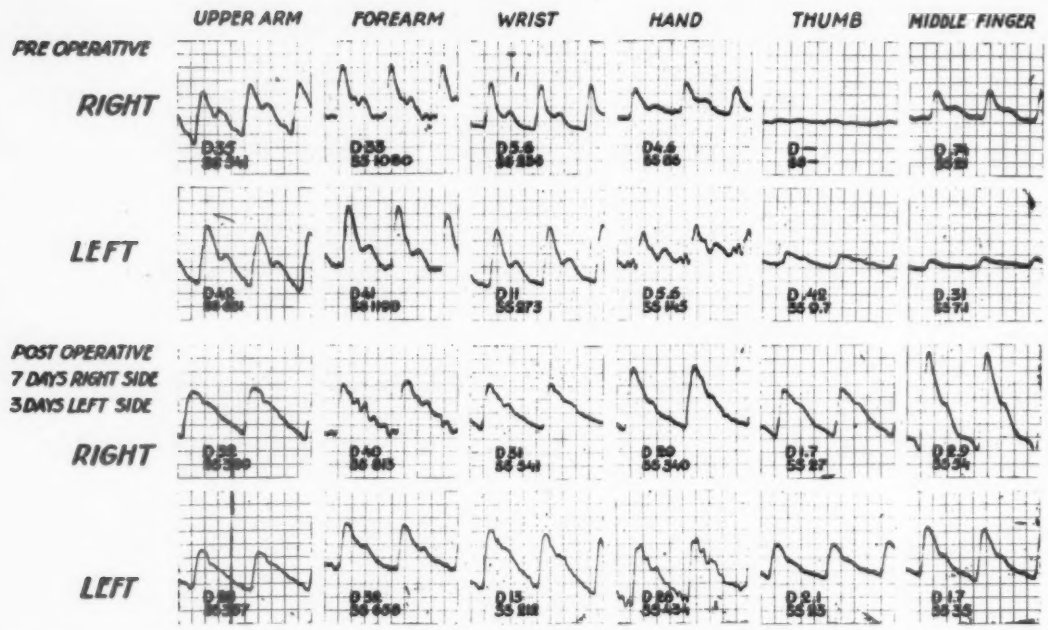

FIG. 6. *Raynaud's disease.* Response to sympathectomy in the same patient as in Figure 5. The preoperative survey was made at room temperature. The vasoconstriction at the wrist, hand and digits is overcome by the operation. These early findings have been maintained over the subsequent year.

that the induced constriction no longer obliterated the distal pulses.

An example of the relief of vasoconstriction by the administration of a vasodilator drug (Ilidar®) is shown in Figure 7.

DISEASES PREDOMINANTLY ORGANIC

Distal Arteriosclerosis: The varying severity of the arteriosclerotic lesion is reflected in the pulse, which shows a more or less severe deformity distal to the obstruction, which we have termed the "poststenotic" pulse. It is characterized by a diminution in mean pulse deflection and systolic slope, a loss of the dicrotic notch and the presence of aberrant vibrations close to the site of obstruction.

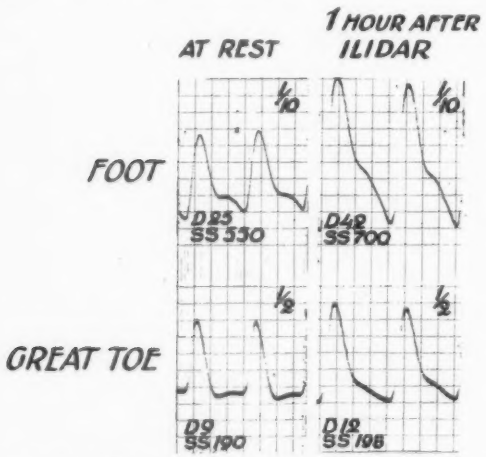

FIG. 7. *Effect of the vasodilating drug Ilidar.* The patient is a twenty-five year old woman with symptoms suggestive of early scleroderma.

When the disease is diffuse in the limb, the changes will be progressively more pronounced as pulses are recorded at successively more distal levels. Because of the sensitivity of the instrument, a pulse trace may be discerned even when the finger fails to detect it. Not uncommonly, however, no pulse can be recorded in the toe.

The reactive hyperemia in diffuse arteriosclerosis is modified according to the severity of occlusion. The reaction may be reduced, absent, or finally, may show an inverse reaction, the pulse becoming smaller or disappearing after release of the occluding cuff (Fig. 8). These findings are similar to those reported by Kondo and his associates.[3]

Aortic Obstruction: Arteriosclerotic obstruction localized to high levels, as at the aorta, and, to some degree, at lower sites such as the femoral artery, gives rise to the characteristic poststenotic pulses below the obstruction; however, as successively lower levels are examined, somewhat less distorted pulses are found in the

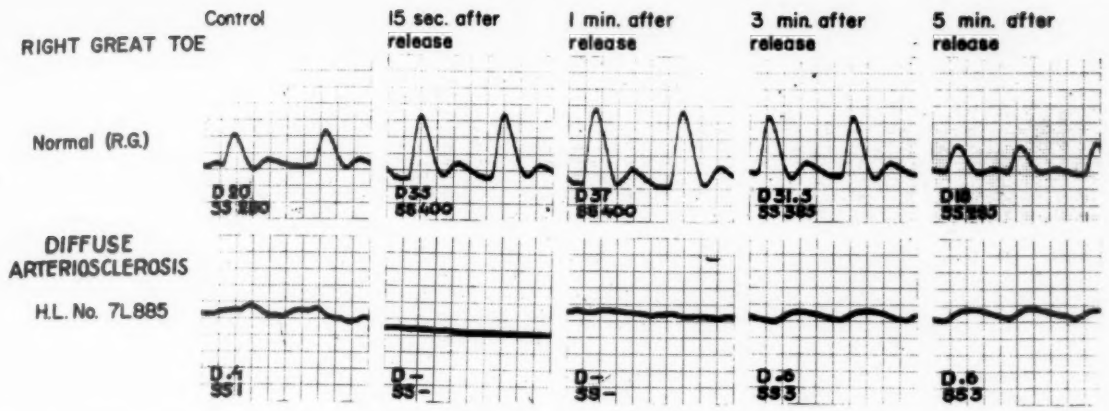

FIG. 8. *Distal arteriosclerosis.* Reactive hyperemia in a patient with "diffuse" arteriosclerosis, compared with the normal. Instead of vasodilatation, the inverse reaction of constriction occurs on release of the occluding cuff, followed by a delayed and minimal dilatation.

foot and toe (Fig. 9). The conditions apparently responsible for this finding are a good collateral around the obstruction, open and elastic vessels distally and finally the good sensitivity of the instrument and the fact that it depends on volume change during a pulsation rather than on level of pressure. Reactive hyperemia in these instances may also be quite normal in pattern (Fig. 9), a fact recognized by Pickering.[2]

There is a wide range of reactivity to cold in patients with arteriosclerosis. In general there is an exaggeration to the test, to the point, in some instances, of complete obliteration of the pulse, although with faster recovery than in Raynaud's disease.

Localization of Other Types of Arterial Obstruction: The technic of localization of other types of organic obstruction is much the same as for arteriosclerosis, the survey of pulses at rest as well as the reactive hyperemia test being of importance. A good example was seen in a patient with panarteritis nodosa, with extreme limitation of pulses in all the toes of one foot, but with good pedal pulses. The reactive hyperemia test was normal in the foot, but the toes were unresponsive. The nature of the process was shown at autopsy.

It is possible to demonstrate obstruction in even smaller segments of the arterial tree. An example is shown in Figure 10 of a patient with such a lesion of uncertain etiology, af-

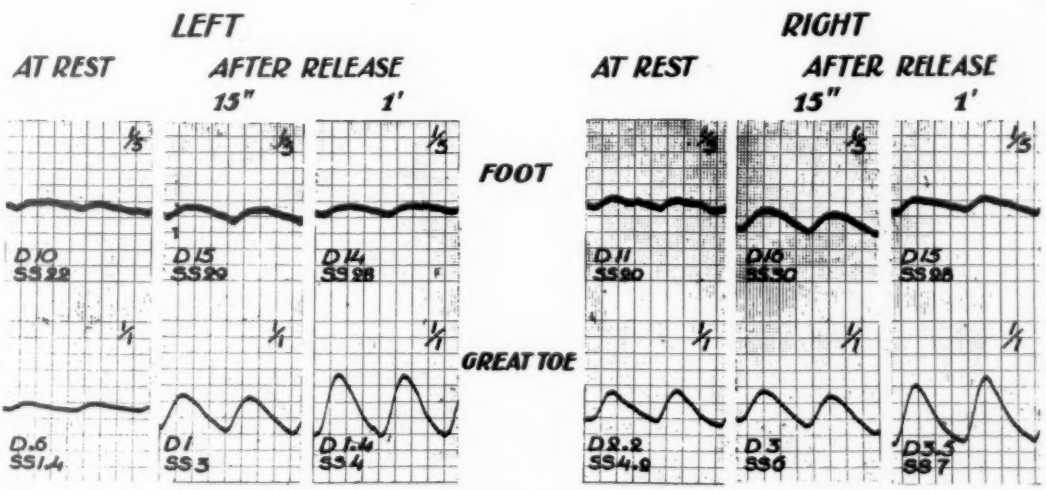

FIG. 9. *Arteriosclerosis, aortic bifurcation block.* Reactive hyperemia in a patient with arteriosclerotic obstruction, localized to the aortic bifurcation. The response resembles that of the normal, indicating freedom of disease in the acral parts. Endarterectomy restored excellent pedal pulses.

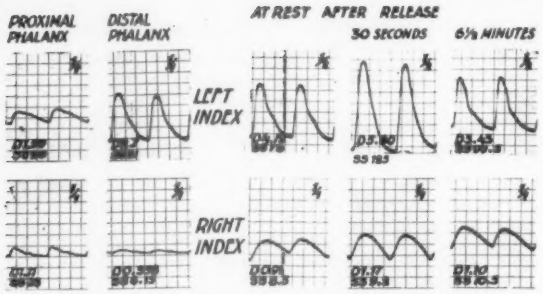

FIG. 10. *Undetermined arterial disease. Left,* ischemia involving particularly the distal half of the right index finger. The exaggerated pulse over the terminal part of the left index finger is a usual and normal finding. *Right,* while the nature of the disease in this patient is uncertain, the reactive hyperemia test suggests that vasoconstriction plays an important role.

fecting mainly the distal part of the digital arteries of a single finger. The reactive hyperemia test in this patient suggests that spasm plays a large role, since the hyperemic rise is as great proportionately in the diseased as in the healthy finger.

Scleroderma: Scleroderma is a most varied category as regards the presence of organic change in the arteries and of vasospasm. In early cases, there may be no circulatory changes whatever, or reactions may be present duplicating what is found in Raynaud's disease, that is, extreme reaction to cold with disappearance of the pulse, with or without resting vasoconstriction, and a normal reactive hyperemia.

As the collagenous hyperplasia becomes pronounced and arterial occlusion is added, the pulses become much reduced at rest, reactive hyperemia is limited, with cold sensitivity still a pronounced feature. The impression is that rigidity of the tissues affects the capillaries much more readily than the arteries, since a great limitation of the pulses at rest or in hyperemia is found only when the disease has reached a point of great severity (Fig. 11).

COMMENTS

The degree of response in reactive hyperemia is seen to depend upon three factors: (1) The degree of pre-existing vasoconstriction which the test may overcome; (2) a good level of blood inflow to the distal parts, either through a normal major artery or via good collaterals and (3) patent and dilatable acral vessels.

When a good pulse exists as far distally as the wrist or ankle in the resting state, a good hyperemic response in the hand or foot confirms that pre-existing ischemia was due to spasm; while a poor response indicates the presence of acral organic disease. A low absolute level of response may be due to persistent vasospasm, since this maneuver, like any other designed to overcome spasm, cannot be assumed to do it "completely" in any given case.

It is necessary to note that the organic lesion of arteriosclerosis is uncommonly limited to a high obstruction. Study from this laboratory has demonstrated multiple obstructions in the small arteries of the foot in non-diabetic as well as in diabetic subjects.[4] The degree of this small vessel lesion determines whether a particular involvement shall be termed "localized" or "diffuse." There are, of course, some patients with arteriosclerosis in whom a high degree of vascular tone is significant. In such instances the configuration of the pulse is not greatly distorted, and the reduced deflection can be largely overcome by reactive hyperemia. In most patients with arteriosclerosis, the factor of tonus affects the outcome of the test much less than do the factors of arterial inflow and acral vessel patency. We have found that an adequate reactive hyperemia affords a good

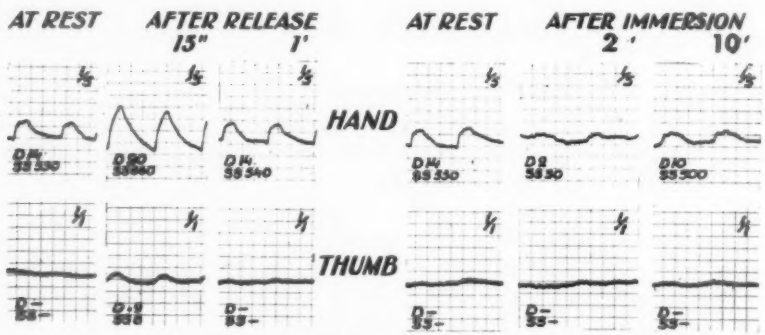

FIG. 11. *Reactions in advanced scleroderma. Left,* the limited response in reactive hyperemia and *right,* the striking constriction after cold immersion are prominent features.

prognosis in these patients, particularly as to the outcome of either a sympathectomy or a reconstructive operation.[5]

Experience with the cold immersion test in a variety of subjects re-emphasizes that vasoconstriction is a universal response to exposure to cold. The normal range of response is so great that there exists no result absolutely diagnostic of Raynaud's disease. The test must be interpreted in the light of the clinical picture.

While we postulate a special sensitivity to cold in Raynaud's disease, no such idiosyncracy is necessary to explain the Raynaud's phenomenon occasionally seen in a frankly organic disease such as arteriosclerosis. In these patients, a reduction of local arterial pressure already exists. Particularly when the disease affects the upper extremity, where vasomotor reactions are normally acute, the vasoconstriction on exposure to cold may easily cause a further drop in the acral arterial pressure to a level below the critical closing pressure, with precipitation of blanching.

For the demonstration of cutaneous vasoconstriction, pulse registration must be supplemented by some other means of study, since the sensing cuff embraces the entire cross section of the limb at any one site. For this aspect of study, measurement of skin temperature continues to be an invaluable adjunct.

Conclusions

Patency and vasomotor reactivity of the peripheral arteries can be simply determined by pulse registration before and after the use of vasodilatory and vasoconstrictive maneuvers.

Vasodilatation is produced by reactive hyperemia after cuff occlusion, vasoconstriction by cold immersion of the part.

The special value of the method lies in the fact that the pulse trace reflects deep as well as superficial changes, the examination can be made from proximal limb levels as readily as from the digits, and heating and cooling can be tested directly on the affected part.

The method readily differentiates functional from organic occlusion, although the superficial location of vasospasm must be verified by measurement of skin temperature.

In arteriosclerosis, the method helps in identifying distal diffuse involvement.

While vasoconstriction is a universal reaction to cold, patients with so-called sensitivity to cold show an exaggerated and prolonged response.

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The Digital Circulation in Raynaud's Disease*

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THE nature of the circulatory derangement in Raynaud's disease is still the subject of some disagreement. In his original description of the condition, Raynaud[1,2] found that the digital blood vessels were normal. He called the disease a "neurosis" because he presumed that these blood vessels went into spasm due to nervous stimulation. In 1893 Hutchinson[3] pointed out that the attacks which Raynaud described could be observed in patients with structural disease of the digital arteries, such as scleroderma, and he distinguished this type of response from Raynaud's *disease* by calling such episodes examples of Raynaud's *phenomenon*. Subsequently many other diseases associated with structural changes within digital or more proximal arteries were found to be capable of producing Raynaud's phenomenon. These diseases included scalenus anticus syndrome, thromboangiitis obliterans, arteriosclerosis obliterans, periarteritis nodosa, lupus erythematosus and cryoglobulinemia, among others.

In 1934, however, Lewis and Pickering[4,5] studied cases clinically diagnosed as Raynaud's disease and found evidence from physiologic observations, confirmed subsequently by pathologic studies, that this disease was often attributable to a "local fault" in the blood vessels. By this they meant that there was often local digital arteriopathy of either mild or extreme degree in Raynaud's disease, regardless of the neurogenic factor. These observations were in agreement with other pathologic studies[6–8] as well as with the results of *in vivo* arteriography,[9] by means of which it was observed that some but not all patients with Raynaud's disease had obstructed digital arteries. The pathologic changes observed in the arteries consisted of intimal proliferation, with or without superimposed thrombosis, followed by organization and recanalization. It was not clear from the data, however, whether these arterial changes arose *de novo* or developed as a consequence of Raynaud attacks in persons with initially normal digital blood vessels, and there is still some difference of opinion on this question. Lewis[5] could find no clear-cut medial hypertrophy, whereas Goetz[6] believed such hypertrophy to be unequivocal. The number of cases reported, however, is too small to decide this point.

In 1957 increased neurogenic vasoconstriction of the digital blood vessels of patients with primary or essential hypertension was demonstrated.[10] It was subsequently shown[11] that this was largely attributable to increased sensitivity to l-norepinephrine (NE), as produced by normal sympathetic neural discharge, rather than to increased neural discharge as such. It was also found[12] that increased vascular sensitivity to NE could be demonstrated in Cushing's syndrome, occurring naturally because of adrenal cortical hyperplasia or adenoma formation, or induced by the administration of cortisone, prednisone or adrenocorticotropic hormone (ACTH). Since the effect appeared after a relatively short period of hormone administration and without associated hypertension, it was believed that the steroids were inhibiting an enzyme responsible in vascular smooth muscle for the immediate pressor inactivation of NE, and that primary or essential hypertension was caused by a hereditary deficit of the same enzyme.[13] The possibility could not be excluded, however, that some of the increased sensitivity to NE was caused by vascular smooth muscle hypertrophy, especially late in the course of hypertension or Cushing's syndrome.

It therefore seemed of interest to study the

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digital circulation in patients with Raynaud's disease. For one thing, mechanisms for vasoconstriction might differ from those observed in hypertension and Cushing's syndrome; and also, some light might be shed on the relation of vascular smooth muscle hypertrophy to vascular sensitivity to NE.

Methods

Digital circulatory studies were completed in twenty patients with Raynaud's disease and compared with those in twenty-three normotensive subjects without vascular disease. No patient was included in the study who had any disease which was capable of producing Raynaud's phenomenon such as generalized scleroderma or thromboangiitis obliterans. Digital arterial blood pressure was measured with a Gaertner capsule using the flush-throb technic, and digital blood flow was determined calorimetrically.

Measurements of blood pressure and flow were made during three separate phases: (A) after vasodilatation produced by 30 to 45 minutes of indirect heating, supplemented by the intravenous injection of 8 mg./kg. of a ganglion blocking drug, 2,6 dimethyl-1,1-diethyl piperidinium bromide (SC 1950); (B) before vasodilatation, in recumbency and at rest with standard covering and at a room temperature between 26° and 29°C., and (C) during maintenance of indirect heating and intravenous infusion with a pump of additional SC 1950 and NE at a concentration and rate sufficient to raise brachial arterial blood pressure to its level in phase (B) or slightly above that level. The solute concentrations in the infused solution were glucose 50 mg./cc., l-norepinephrine bitartrate 0.0122 mg./cc. and SC 1950 0.09 mg./cc. In eight cases only phase (A) and (B) were completed, whereas in two cases only phase (A) and (C) were completed. In the remaining ten cases the three phases were completed. Most often (nine cases) the three phases were finished during one session, whereas in one case two sessions were needed.

Effective mean digital arterial blood pressure was obtained by adding one-third of the pulse pressure to the diastolic pressure and subtracting from this, corrections for venous pressure and pressure axis intercept. The ratios between flows and effective mean digital arterial blood pressures were converted into measurements of radius equivalents by procedures previously described,[10] and these values together with the pressures were used to determine the *work of vasoconstriction.* This was calculated not only for the resting state (phase B), but also per milligram of NE infused per minute (phase C), in both instances using the radius equivalent in phase A, the vasodilated state, as the basic value for intrinsic vascular caliber.

Results

It became apparent that the cases could be divided into two groups on the basis of the intrinsic vascular caliber or radius equivalent in phase A, that is, after reflex dilatation (Table I). In one of these groups the values were normal, whereas in the other they were definitely below the 95 per cent range for normal subjects. In the first group the values for vasomotor tone in the resting state (work of vasoconstriction) were usually high, whereas in the latter group they were usually normal. None of these patients was in a frank Raynaud attack at the time of testing. With one exception, there was no significant increase in norepinephrine sensitivity in any of the patients tested regardless of the group into which they fell.

Comments

One may interpret these results to mean that the blood vessels in Raynaud's disease are always of normal caliber intrinsically but that we failed to obtain complete inhibition of vasomotor tone in about half the cases and that the work of vasoconstriction values was therefore low in this group. Against this view is the experience that the procedure produces about 90 per cent inhibition of vasomotor tone in normotensive and even in hypertensive subjects when vasoconstriction is increased.[10] Also it would negate the finding of vascular obstruction as demonstrated by arteriography and at autopsy in many patients with Raynaud's disease. In such cases it is known that collateral circulation is rarely adequate to compensate completely for the obstruction.

It is more likely, therefore, that, as many workers have suggested,[5,14–16] there are two types of Raynaud's disease, one with and one without digital vascular obstruction and that exaggerated vasomotor tone is found largely in the latter group. One cannot determine from these studies whether vascular obstruction can be a consequence of Raynaud attacks in a subject with normal vessels, or whether vascular obstruction can occur *de novo* and be followed by Raynaud attacks. Perhaps either sequence of events can take place, although it is difficult, if the former sequence obtains, to see why vasomotor tone would not continue to be increased regardless of whether thrombosis or intimal proliferation had supervened.

Mechanism of Vasoconstriction: The fact that there is no significant increase in sensitivity to NE in Raynaud's disease, such as occurs in Cushing's syndrome[12] or in primary hypertension,[11] indicates that the mechanism for vasoconstriction in Raynaud's disease differs

TABLE I
Digital Circulatory Studies in Raynaud's Disease

Patient	Age (yr.) and Sex	Phase*	Brachial Blood Pressure (mm.Hg)		Digital Blood Pressure (mm. Hg)		Effective Mean Digital Blood Pressure (mm. Hg)	Digital Blood Flow (cc./cm.² skin/min.)	Radius Equivalent (10^{-2} cm.)	Work of Vasoconstriction (10^3 erg.)	Rate of NE Infusion (10^{-2} mg./min.)	Work per mg.NE per Minute (10^3 erg./mg./min.)
			Systolic	Diastolic	Systolic	Diastolic						
95% Range for Normal Subjects		A	85–123	51–79	67–107	32–72	36–80	0.21–0.37	2.9–3.7			
		B	96–140	52–88	70–138	39–91	50–106	0.08–0.32	2.6–3.4	0.30–3.1		
		C	130–192	72–120	100–168	65–145	61–121	0.12–0.36	2.4–3.2	0.30–1.42	1.0–4.2	13–52
Patients with Raynaud's Disease with Intrinsically Normal (Unobstructed) Digital Arteries												
I. M.	27,F	A	98	62	87	48	52	0.21	2.9	...	...	...
		B	110	68	95	61	70	0.04	1.8	5.3	...	...
		C	130	85	114	74	78	0.22	2.8	0.41	1.2	23
C. T.	42,F	A	90	60	76	52	54	0.33	3.2	...	...	...
		B	120	74	100	74	79	0.09	2.4	3.2	...	...
		C	136	86	122	82	86	0.22	2.6	0.37	0.7	46
M. C.	23,F	A	90	60	80	50	48	0.30	3.3	...	...	...
		B	110	70	106	70	82	0.01	1.7	8.1	...	...
		C	...	...	...	...	...	...	...	...	...	...
S. P.	42,F	A	90	58	64	40	35	0.30	3.5	...	...	...
		B	100	64	86	56	61	0.13	2.9	2.3	...	...
		C	130	74	110	66	61	0.25	3.2	1.1	2.2	32
R. F.	21,F	A	106	66	100	60	60	0.32	3.1	...	...	...
		B	120	70	...	...	...	...	...	...	...	...
		C	146	90	130	84	89	0.33	3.0	0.52	1.5	29
A. M.	39,F	A	86	46	58	20	28	0.12	3.0	...	...	...
		B	102	60	88	48	52	0.11	2.6	1.1	...	...
		C	...	...	...	...	...	...	...	...	...	...
F. C.	47,F	A	96	66	71	39	42	0.20	3.0	...	...	...
		B	124	74	112	62	79	0.01	1.5	5.6	...	...
		C	144	86	120	72	80	0.19	2.8	0.76	1.3	49
L. M.	23,F	A	100	60	85	50	50	0.28	3.2	...	...	...
		B	120	70	90	60	68	0.06	2.6	2.8	...	...
		C	...	...	...	...	...	...	...	...	...	...
M. C.	39,F	A	96	62	92	54	52	0.36	3.3	...	...	...
		B	120	66	104	58	72	0.03	2.4	4.8	...	...
		C	146	88	134	80	88	0.24	2.9	2.0	3.1	65
D. B.	62,M	A	110	70	84	60	55	0.32	3.2	...	...	...
		B	126	76	120	74	84	0.11	2.6	3.2	...	...
		C	146	80	110	64	68	0.27	3.1	0.46	0.83	55
L. K.	53,F	A	100	58	88	48	51	0.24	3.0	...	...	...
		B	106	64	98	56	69	0.03	2.2	3.9	...	...
		C	150	80	134	78	88	0.24	2.8	0.84	1.4	56
Patients with Raynaud's Disease with Obstructed Digital Arteries												
S. E.	35,M	A	96	80	94	73	77	0.07	2.1	...	...	...
		B	104	82	103	79	89	0.03	1.7	0.13	...	...
		C	128	90	126	91	100	0.08	2.0	0.18	0.78	17
L. S.	65,F	A	76	50	68	50	51	0.11	2.5	...	...	...
		B	130	80	74	60	64	0.02	2.0	2.1	...	...
		C	160	98	124	84	95	0.05	2.1	1.1	3.6	33
H. P.	21,F	A	106	64	100	52	63	0.14	2.5	...	...	...
		B	110	66	86	56	65	0.03	2.0	1.4	...	...
		C	150	100	138	90	104	0.04	2.2	2.4	2.1	97
J. F.	56,M	A	96	74	92	72	74	0.20	2.6	...	...	...
		B	120	78	...	...	...	...	...	...	...	...
		C	146	86	136	80	92	0.18	2.5	0.54	2.1	20
N. S.	24,F	A	108	70	110	80	80	0.25	2.7	...	...	...
		B	120	80	130	90	101	0.05	2.1	5.1	...	...
		C	...	...	...	...	...	...	...	...	...	...
C. J.	37,F	A	110	70	80	62	64	0.10	2.3	...	...	...
		B	130	78	104	74	82	0.06	2.1	0.84	...	...
		C	...	...	...	...	...	...	...	...	...	...
A. E.	44,F	A	86	44	68	41	46	0.10	2.5	...	...	...
		B	112	72	96	61	70	0.06	2.2	1.0	...	...
		C	...	...	...	...	...	...	...	...	...	...
L. S.	50,F	A	90	64	60	24	35	0.03	2.1	...	...	...
		B	114	70	100	38	58	0.02	1.7	0.56	...	...
		C	...	...	...	...	...	...	...	...	...	...
N. J.	27,F	A	114	70	82	62	60	0.21	2.8	...	...	...
		B	126	70	96	68	69	0.17	2.7	0.53	...	...
		C	...	...	...	...	...	...	...	...	...	...

*A = After vasodilatation by indirect heating and chemical ganglionic blockade. B = Before vasodilatation by indirect heating and chemical ganglionic blockade. C = After vasodilatation by indirect heating and chemical ganglionic blockade together with NE infusion.

from that in the other diseases. In the cases of Raynaud's disease without vascular obstruction, the only remaining mechanism which can account for the heightened vasomotor tone is increased neural discharge. It would seem likely under such circumstances that smooth muscle hypertrophy of arteriolar walls would occur, although this is not as yet unequivocally established pathologically. If it does occur in these cases, it gives further weight to the thesis that vascular smooth muscle hypertrophy is not primarily responsible for increased vascular sensitivity to NE as seen in primary hypertension and Cushing's syndrome. In a negative way, therefore, it would give additional support to the theory that hydroxycorticosteroids inhibit the enzyme in blood vessels responsible for immediate pressor degradation of NE and that a hereditary deficit in this enzyme system is the cause of primary hypertension.

Mechanism of Raynaud Attack: It is of some interest to speculate on the mechanism of the Raynaud attack itself. Modern physiologic doctrine holds that a blood vessel will close suddenly if the pressure within the vessel becomes lower than the tension created within its wall by the tone of its smooth muscle.[17] The pressure level at the point of closure has been called the critical closing pressure. It is clear that any factor tending to decrease intravascular pressure or increase vasomotor tone would tend to bring the blood vessel closer to this point of sudden closure. In the patients with obstructive arteriopathy, of digital or even of more proximal arteries, it is most likely that pressure beyond the obstruction becomes so low that even ordinary grades of vasomotor tone can produce closure, whereas in the group with intrinsically normal blood vessels, vasomotor tone is sufficiently increased so that it can exceed the critical point even in patients with relatively normal blood pressure. The effect on distal blood pressure produced by vasospastic arterial narrowing would be an additional factor precipitating closure. It is still unclear, however, as to what distinguishes a normal decrease in blood flow, as for example, a response to cold, from complete cessation of flow in a Raynaud attack. In the latter, the change occurs perhaps because the digital arteries themselves close, whereas in the former, a small trickle of blood still perfuses the capillaries, probably because only the arteriovenous anastomoses close completely.

It has been shown recently by Edwards[18] that, as in Raynaud's disease, in acrocyanosis there are also two types of patients, namely, those with and those without vascular obstruction. The symptom of acrocyanosis is produced by decreased blood flow through the skin of the extremities, with increased extraction of oxygen from oxyhemoglobin and hence an excess of reduced hemoglobin. Since the color is seen largely in the cutaneous venules, it will tend to be absent if this bed is relatively constricted and will be intensified if it is dilated, as it tends to become when anoxia is chronic.

Proposed Nomenclature: It can be seen from all this that the nomenclature for these conditions is confusing and out of date. It is proposed that we speak of (1) obstructive digital arteriopathy, and (2) neurogenic digital arterial spasm. Each of these could remain unqualified or qualified by (a) with Raynaud attacks or (b) with acrocyanosis, or both. Cases of so-called Raynaud's phenomenon attributable to cervical rib, for example, would become obstructive subclavian arteriopathy produced by cervical rib, with or without Raynaud attacks, as the case may be. In this way, Raynaud's name would be preserved for the clinical syndrome and the terms "Raynaud's phenomenon" or "disease" abandoned, together with the isolated term, "acrocyanosis." The attacks in old people of white fingers without numbness and subsequent cyanosis should also be brought under this grouping as obstructive digital arteriopathy due to arteriosclerosis with Raynaud attacks, since these cases probably represent a minor variant of the syndrome described by Raynaud. At any rate, pathology and etiology would be emphasized and vagueness banished.

Summary and Conclusions

1. Blood pressure and digital blood flow were studied in twenty patients with Raynaud's disease at rest under standardized conditions, after vasodilatation, and after vasoconstriction produced by intravenously infused l-norepinephrine (NE).

2. The patients fell into two groups: (1) those with digital vascular obstruction and normal vasomotor tone, and (2) those without obstruction but with heightened vasomotor tone. In neither group was sensitivity to NE increased.

3. These findings suggest that Raynaud attacks are produced either by vascular obstruction acted upon by normal vasomotor

tone or by heightened vasomotor tone acting on otherwise normal blood vessels, and that in the latter group the heightened tone is produced by increased sympathetic neural discharge. If there is smooth muscle hypertrophy in Raynaud's disease, moreover, this factor does not produce an increase in NE sensitivity.

4. A new nomenclature is proposed for Raynaud's disease and phenomenon, and acrocyanosis.

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Physiologic Aspects of Intravascular Clotting*

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DESPITE, or perhaps because of, advances in medical knowledge, the problem of thromboembolism is as important today as it has ever been. Whether intravascular clotting is to be considered on the increase or decrease depends to a great extent on whose statistics one accepts. Some of the more recent factors considered to be contributing to its occurrence may be: the increasing longevity of the population in general, the tendency of the surgeon to undertake more extensive exploration, resection, repair and transplantation in all areas of the body, the more involved diagnostic procedures, the extensive therapeutic measures now in use, particularly the battery of new drugs and the widespread use of intravascular infusions of many types and substances.

More than one hundred years ago Virchow[1] suggested that the principal factors predisposing to thrombosis are: (1) changes in blood vessel walls, (2) alterations in blood flow and/or (3) physical and chemical changes in the blood. Except in the matter of detail, most authorities today will agree with these precepts.

Changes in blood vessel walls may occur as a result of (1) trauma (mechanical, thermal, chemical, bacterial), (2) degeneration, particularly atheromatous, (3) nervous influences, such as those seen in Raynaud's disease and spasm of non-specific nature and (4) other changes occurring in conditions such as thromboangiitis obliterans, pulseless disease, polyarteritis nodosa and changes in mast cells, qualitative and quantitative.

Alterations in blood flow are those primarily of stasis which depend upon such influences as gravity, physical activity or lack of it, cardiac decompensation, tumors—benign and malignant, scarring and varicosities.

Physical and chemical changes in the blood include (1) hemoconcentration resulting from hemorrhage, shock, burns, plasma and serum loss, dehydration and agglutination of solid elements, (2) alterations resulting from low temperatures (cryoglobulinemia) (of interest is the low incidence of thrombophlebitis in warm climates), (3) those resulting from metabolic disorders, tissue destruction, anemias, tumors or inflammations of the pancreas, ingestion of fats, drugs (antibiotics, methylxanthines, steroids, tranquilizers, digitalis, Adrenalin®, vitamins C and E) and (4) the protean alterations brought about by intravenous infusions.

Lack of Methods for Anticipating Intravascular Clotting

Much has been written on methods for anticipating thrombosis, most of which may be grouped into two categories: (1) those for measuring changes in the coagulation time of whole blood or plasma and (2) those for measuring alterations in the activities of clotting or anticlotting factors.

Differences in clotting times of blood or plasma have been studied under a variety of conditions such as (1) after dilution, (2) in the absence of contact with wettable surfaces, (3) after removal of solid elements, (4) with the use of various mechanical devices (the thromboelastograph being one of the more recent and complicated ones), and (5) following the addition of anticoagulants such as citrate or oxalate and subsequent recalcification (Howell coagulation time), heparin—*in vivo* and *in vitro*, tissue juice (prothrombin time) and snake venoms (viper venom clotting time).

Variations in clotting and anticlotting factors in the thrombotic and/or postoperative period have been reported by a number of authors and included among these are most of the known factors. Many of these reports have been conflicting and unanimity of opinion on a reliable

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method for predicting thrombosis is still lacking.[2,3]

The Problem

It is altogether likely that thrombosis in different patients is not necessarily the result of identical changes in their broad respective coagulation mechanisms. It is probable that these changes occur as the result of alterations in a number of factors in each instance and that while some of the latter may be basically the same in all patients, they may be of a different nature in others.

There is reason to believe that, in the majority of instances, the chemical changes in the blood may be of greater importance than alterations in the vessel walls or rates of blood flow. It is also likely that these chemical alterations include changes affecting various aspects of coagulation such as the formation of thrombin, its inhibition or inactivation and lastly, the over-all activity of the fibrinolytic system. It appears likely that blood coagulation is a dynamic process, a limited amount of clotting presumably occurring continuously and, that under normal conditions, various opposing factors prevent the excessive accumulation of the products of this process.[4]

The thrombotic tendency is not only important as such, but in certain clinical conditions may actually be responsible for the development of severe hemorrhagic diatheses. These may develop during pregnancy or as a result of shock, burns, surgical trauma, transfusion reactions and malignancy.[5–8]

Another area in which intravascular clotting may be a contributing factor to an apparently unrelated condition is that of generalized atherosclerosis. Various aspects of this relationship will be discussed in a later section of this paper.

The Mechanism of Blood Coagulation

The mechanism of blood coagulation as described by Morawitz[9] more than a half century ago is still essentially valid. According to this concept prothrombin, in the presence of thromboplastin and calcium, is converted to thrombin. The latter, in turn, changes fibrinogen to fibrin, the insoluble gel.

This theory involved four basic factors. With the end of World War II the picture assumed new proportions as an increasing number of new "factors" was described, leading to a continually changing and ever more complicated picture. Despite this apparent confusion, however, the existence of certain "factors" has been sufficiently well documented by this time to warrant a brief discussion of their role in the clotting mechanism.

It appears now that thromboplastin is formed not only as a result of tissue damage, but may also develop in blood itself through the interaction of certain plasma proteins and cellular components. "Intrinsic thromboplastin" was originally thought to result from the interaction of antihemophilic globulin (AHG), plasma thromboplastin component (PTC), platelets and calcium.[10] This interaction has been shown to occur in several stages[11] and its final product appears to be a phospholipoprotein.[12] Recent evidence suggests that, in addition to the aforementioned factors, plasma Ac-globulin (factor V) is also essential to the evolution of the final prothrombin-converting principle.[13] Further implicated in the generation of intrinsic thromboplastin have been plasma thromboplastin antecedent (PTA),[14] factor X[15] and Stuart factor.[16] One of the more recently described coagulation factors is proconvertin[17] (SPCA, factor VII, autoprothrombin I). Although it now appears that this factor is not involved in the formation of intrinsic thromboplastin and, although there is some doubt as to whether or not it is essential to the *generation* of thrombin,[18] it apparently is important as an accelerator of the latter's physiologic formation.

The action of thrombin on fibrinogen has been shown to be of a proteolytic nature and to involve the splitting off of two or more peptides, followed by the polymerization of this altered fibrinogen.[19]

It appears that both thromboplastin and thrombin are rapidly neutralized or inactivated in plasma and there is evidence to suggest that such neutralization may occur by direct inhibition[20,21] as well as by actual destruction[22–25] of these two factors. Of the clot-inhibiting factors, heparin probably plays one of the more catholic roles operating at various stages of the coagulation mechanism.[26–30]

As stated earlier, it appears reasonable to consider clotting as a dynamic process including a mechanism for the removal of the final product, fibrin. This fibrinolytic activity can be readily demonstrated in normal patients and may become excessive in various clinical states. It has been suggested that, as in the case of thromboplastin, the organism also possesses two mechanisms for the production of active fibrinolysin (plasmin).[4] Thus the plasma precursor, profibrinolysin (plasminogen) may be acted on

by a tissue activator as well as by an activator formed in plasma itself.

Various suggestions have been advanced as to the mechanism by which abnormal intravascular clotting is initiated.[31–33] Although there are differences of opinion regarding the sequence of events, there appears to be general agreement concerning the importance of endothelial injury and resulting platelet alterations.

Physical Factors

Among the physical factors considered to promote intravascular clotting are: (1) injury to the vascular endothelium with the elaboration of a "granular cement,"[34] local platelet concentration and the sequence of events set up by such concentration,[31,35] (2) sludging of blood which may occur under a number of conditions such as infection, excessive heat or cold, metabolic disorders and others,[36–38] (3) lack of muscular exercise accompanied by decreased blood flow and possible decreased fibrinolysis,[39] (4) lowering of tissue temperatures with cryoprotein precipitation and accompanying vascular narrowing,[40,41] (5) regional body radiation[42,43] and (6) a positively charged vascular wall.[44]

In individual cases the role of some of these factors may be prominent but in the majority of instances of thromboembolism their relative importance will be difficult to assess.

The Effect of Drugs on the Clotting Mechanism

Clot-Inhibiting Drugs: Of the drugs inhibiting clotting activity and thus reducing the tendency toward intravascular clotting, *heparin* and the *prothrombin-depressants* form by far the most important group. Heparin is extremely versatile in its effects on various factors, influencing all the stages of the clotting mechanism at one or more points. The discovery of the multiple roles of this substance has apparently only begun.

Until recently, the prothrombin-depressants were considered to affect prothrombin primarily. A number of investigators, however, have reported effects also on factors other than prothrombin. Among these are the accelerators, factor VII[45] and, to a lesser degree, factor V.[46,47] Plasma thromboplastin component (factor IX, Christmas factor), factor X and plasma thromboplastin antecedent have been found by a number of workers to be depressed as a result of anticoagulant therapy.[15,48–55] Furthermore, the more recently described Hageman factor[56] and Stuart-Prower factor[57] have also been reported to be depressed by these drugs. In addition to their inhibitory action on clotting activity, the anticoagulants, both heparin and the prothrombin-depressants, promote the lysis of the clot, once formed.[8,30,58]

A further physiologic effect of prothrombin-depressants, not necessarily related to their anticoagulant properties and yet possibly not entirely divorced from them, is their uricosuric action.[59–61]

In the listing of drugs influencing the clotting mechanism, salicylates, because of their structural similarity to coumarins, should be mentioned as contributing, under certain conditions, to hypoprothrombinemia.[8,62,63]

Clot-Promoting Drugs: Among the drugs reported to increase the clotting activity of blood are the *methylxanthines*, caffeine, theobromine, theophyllin and aminophyllin.[8,64,65] Their effects may be due, at least in part, to an increase in plasma Ac-globulin concentration.[65]

The *cardiac glycosides* have also been said to accelerate the clotting mechanism, although, particularly in the case of digitalis, there is lack of agreement on this point. A similar disagreement prevails with respect to the effects of *antibiotics* on the clotting mechanism. (For a detailed discussion see the report of Seegers.[66])

Certain *narcotics and sedatives* reported experimentally to promote blood clotting include morphine, procaine, ethyl morphine, diacetyl morphine, N-allyl morphine and Demerol.[8,67] Certain tranquilizing drugs have been observed to increase the tolerance to prothrombin-depressant drugs in some patients.[8]

Protamine sulfate is well known as a heparin antagonist and perhaps less well known as an inhibitor of fibrinolysin (plasmin).[8,68] Somewhat paradoxical are recent *in vitro* observations indicating that, depending on its concentration, this drug may inhibit the formation and/or action of "blood thromboplastin."[69,70]

Clot-Dissolving Drugs: A number of unrelated drugs are known to enhance the fibrinolytic activity of plasma *in vivo*. Among these are heparin,[30] Adrenalin,[39] serotonin[71] and nicotinic acid.[72]

Endocrine Influences on the Clotting Mechanism

Hypercoagulability of the blood has been observed in patients receiving *corticosteroids*.[73–78] This tendency has been attributed to a number of effects such as thrombocytosis[79] and decreased

plasma fibrinolytic activity,[80,81] a phenomenon which has been put to use therapeutically in certain hemorrhagic conditions.[82] It has been suggested that the decreased fibrinolysis following the administration of corticotropin to animals is mediated through the inhibition of the action of serotonin in promoting fibrinolysin.[83] Of interest in this connection is the finding of increased blood coagulability in persons under stress.[84]

Certain *estrogens*, namely stilbesterol and Premarin,® have been reported to produce similar effects on the clotting mechanism.[85] This action is apparently associated with an increase in plasma prothrombin and Ac-globulin and a decrease in antithrombin.[86] In animals large doses of follicular hormones have been found to retard coagulation in some instances whereas Lutein® and gonadotropin derivatives were found to accelerate it.[87] Another effect of estrogen related to the clotting mechanism is the increase in fibrinolytic activity observed in rats during the late stage of the estrous cycle.[88] In this connection it is of interest that estradiol and testosterone pellet implantations were found to have a marked influence on the fibrinolytic activities in normal and castrated rats of both sexes.[89]

The infusion of *Adrenalin* into human beings and animals is known to increase the coagulability of the blood.[90,91] This has been associated with an increase in the number of circulating platelets and an increase in factor V activity. In splenectomized animals, on the other hand, no changes in the coagulation time and platelet count were observed after such infusion.

Increased Tendency to Thrombosis in Certain Clinical States

Cancer: Patients with pancreatic disease, particularly cancer of the body or tail, have an increased tendency toward thromboembolism.[92–96] Although the reason for this tendency is still obscure it is known that the plasmas of patients with pancreatic disease may have increased levels of trypsin,[97,98] an enzyme known to promote the clotting of blood.[99,100] Tumors of other organs have been similarly incriminated.[101–105] It is noteworthy that in these patients anticoagulant therapy is often ineffectual.[8,106] The clotting mechanism in such patients may be interfered with at more than one point, the authors having observed one patient, aged thirty-five, with a spontaneous prothrombin level (i.e., in the absence of anticoagulant therapy) of 13 per cent and progressive thrombosis to the point of occlusion of major pelvic arteries and gangrene of the buttock and lower part of the leg.

Pregnancy and the Puerperium: Thromboembolic phenomena commonly observed during pregnancy and the postpartum period may be related to changes (for the most part increases) in certain coagulation factors such as prothrombin, factor V, factor VII, thromboplastin and fibrinogen.[107–112] As a result of certain phases of this thrombotic tendency, namely the release of thromboplastin into the blood stream (from placenta ablatio, amniotic embolism or retained fetus), afibrinogenemia may develop and severe or even fatal hemorrhage ensue.[113–117] Another possible influence on the occurrence of thromboembolism during pregnancy may be an increase in the plasma proteolytic activity of such patients.[118]

Thrombotic Thrombocytopenic Purpura: There have been a number of reports of thrombosis accompanying thrombocytopenic purpura[119–122] and various aspects of its pathogenesis have been discussed by several authors.[123–125]

Thrombotic Phenomena Related to Infection: One of the more unusual thrombotic phenomena is gangrene that is occasionally seen following scarlet fever—purpura fulminans.[126–128] Although the physiopathology of this condition is poorly understood it seems probable that the bacterial toxins produce multiple thrombi resulting in fibrinogenopenia,[129,130] Ac-G-deficiency and a rise in antithrombin.[131]

Of interest in this connection is the recent observation that the intravenous injection of bacterial endotoxins accelerates coagulation by a mechanism apparently different from that of the orthodox process involving thromboplastin and thrombin.[132,133] Of importance also, particularly in these days of resistant staphylococcus infections, are studies on the nature of the staphylocoagulase reacting factor and the mechanism by which it produces clotting.[134–137]

Influence of Lipids on the Clotting Mechanism

During the last few years there has been considerable interest concerning the effects on the clotting mechanism of fat intake generally and those of phospholipids specifically. Although a majority of the reports indicates that clotting is accelerated following the ingestion of lipids,[138–150] some investigators have failed to detect such changes.[151,152] Some evidence has been obtained to indicate that the type of fat fed may

account for some of these differences, and that, specifically, the main clot-accelerating factors in fats may be associated with certain types of fatty acids[153–155] and phospholipids.[141,146,156,157] On the other hand, it has also been demonstrated that these same or other phospholipids may, under certain conditions, inhibit coagulation by interfering with thrombin formation.[156,158–162]

In addition to reports concerning effects of fat intake on the over-all coagulation mechanism it has been shown that there are specific effects on individual clotting factors, namely platelets, antihemophilic globulin and plasma thromboplastin component.[163,164] These changes were interpreted to mean that after the ingestion of lipids promoting blood clotting, *the rate of blood thromboplastin formation is increased.* It is interesting that none of these changes occurred in patients receiving adequate dicumarol therapy.

There are also indications that the formation of several prothrombin conversion accelerators from prothrombin may depend on the presence of certain phospholipids and that at least one of these accelerators (plasma thromboplastin component) may actually contain a phospholipid moiety as part of its structure.[165–167]

An inhibition of fibrinolytic activity following the ingestion of fats has also been demonstrated.[168–170] There is evidence that this inhibition varies with the type of fat ingested, the effects produced by saturated fats being considerably more marked than those following the ingestion of unsaturated ones. Furthermore, the reduced fibrinolytic activity can be restored to normal by treatment of the plasma *in vitro* with a variety of fat solvents and the degree of restoration parallels the ability of each solvent to reduce or modify the beta-lipoprotein fraction of the plasma.[171] These observations might invite speculation as to whether or not some of the factors in fats promoting the formation of thrombin may be identical or at least similar to those inhibiting the fibrinolytic system.[172] This speculation derives further support from the finding that platelets, known to be thrombin-promoting, are also antifibrinolytic.[173–176] For a more detailed discussion of the various aspects of the influence of lipid intake on the coagulation mechanism the reader is referred to the report of Hashim and Clancey.[177]

Possible Relation of Clot Formation and Dissolution to Atherogenesis

Knowledge concerning the ability of "fats" under certain conditions to (1) accelerate coagulation and (2) inhibit fibrinolysis has resulted in increased speculation about a possible relationship between blood coagulation and the development of atherosclerosis.[178–185]

In the middle of the last century Rokitansky[186] suggested that the development of atheroma may be related to the formation of mural thrombi. More recently, support for this hypothesis has been presented by the demonstration that material deposited on the arterial endothelium is subsequently incorporated into it by the process of overgrowth.[187–191]

In vitro studies in patients with clinical evidence of ischemic heart disease have indicated the existence of an apparently hyperactive coagulation mechanism.[192] Furthermore, subjects with evidence of atherosclerosis (peripheral, coronary, carotid or basilar arteries) or a positive family history show greater *in vivo* coagulation changes than subjects without apparent atherosclerosis or a family history of it.[193] These coagulation changes consist of increases in the number of circulating platelets and in the activities of plasma and serum plasma thromboplastin component and a decrease in the Russell's viper-venom time. These findings are complemented by the observation that thromboembolic-produced atherosclerosis shows a greater severity and frequency of pulmonary arterial lesions in a group of animals receiving increased fats in their diets than in a parallel one maintained on a low fat diet.[194] Subsequent work from the same laboratory also indicates that a strong affinity exists between thrombi and lipids, that blood lipids rapidly enter thrombi and emboli and that fat remains within them throughout their progression from freshly formed clots to the completely organized fibrous intimal lesions characteristic of atherosclerosis.[195] Additional observations have revealed differences in the severity of the lesions produced depending on the type of fat ingested.[196]

A similar relationship between the type of fat fed and the severity and frequency of the resulting lesions has also been found in swine in the absence of injected clots.[197] The observed coagulation indices were more active and the atherosclerosis was more pronounced in animals fed butter than in those receiving a low fat diet or one in which margarine had been substituted for butter.

Heparin and Plasma Lipids: In recent years a number of observations have been made concerning the altered lipoprotein pattern in atherosclerosis.[198] It has been shown that under

certain conditions heparin prevents the development of atheroma in animals[199] and it was further suggested that it corrects the lipoprotein abnormalities associated with atherosclerosis in man.[200] It has also been reported that blood heparinoid substances are decreased in patients with excessive atheromatous deposits as compared with normal subjects.[201] Mast cells, known to be responsible for the production of heparin,[202] have been found to decrease in numbers with advancing age.[203] The unexpected finding of an increase in perivascular mast cells at the site of human coronary and venous thrombosis[204,205] would seem paradoxical. This finding may be explained, however, by the presence of an increased plasma factor VII activity in patients with recent thromboembolic episodes and the additional fact that factor VII-rich serums have been shown to be antagonistic to the anticoagulant effect of heparin.[206]

Lipoprotein Lipase Activity and Atherosclerosis: The known clearing effect of heparin administration on lipemic plasma may be due to its ability to enhance the activity of lipoprotein lipase, a recently discovered enzyme known to be concerned with various aspects of lipid transport.[207] Deficiencies in the lipoprotein lipase system have been demonstrated in patients with known atherosclerosis,[8,208] coronary artery disease[209] and those with a family history of this latter condition. The finding of diminished protamine titration values in atherosclerotic patients,[210] and the recent observation that thrombin *in vitro* can act as a potent inhibitor of lipoprotein lipase activity, provide additional suggestive links between hypercoagulability and atherogenesis.[211] Of interest in this connection are the reported data suggesting that the lipoprotein lipase co-factor and serum antithrombin may be identical.[212]

Other data would indicate that the absence of clearing activity in patients with atherosclerosis may be due to the presence of an inhibitor rather than to a deficiency of the enzyme as such.[213,214] This theory is further supported by the finding that the clearing activity can be restored by treatment of the plasma with barium sulfate, by heating it to 60°C. and by alteration of its pH.[213] Similar restoration of lipoprotein lipase activity has been observed in the presence of oxalate, citrate and sodium versenate.[8] On the other hand, normal plasma lipoprotein lipase co-factor activity is removed by ether treatment of the plasma, lending support to the possible identical natures of lipoprotein lipase co-factor and antithrombin.[8] An additional link in this chain of evidence is the observation that factor VII, which can be adsorbed on barium sulfate, is an inhibitor of antithrombin[215,216] and the finding that factor VII concentrates prepared from serum are potent inhibitors of the lipoprotein lipase system.[8] Investigations in this interesting field have apparently only begun.

Summary

Various physiologic aspects of the tendency toward intravascular clotting have been presented. The discussion includes comments on the lack of methods for anticipating intravascular clotting; the mechanism of blood coagulation; the effects of physical factors, drugs and endocrine influences on the clotting mechanism; the increased tendency to thrombosis in certain clinical states; the influence of lipids on the clotting mechanism; and the possible relation of formation and dissolution of clots to atherogenesis.

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Some Simple Clinical Tests for the Study of the Arterial Circulation in the Extremities*

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THE DIAGNOSIS of impairment of arterial circulation in the extremities can in most instances be readily made through the use of a number of simple clinical tests, capable of being carried out at bedside or in the office. The purpose of this paper is to describe these various technics and to discuss both their applicability and limitations in the different types of arterial vascular disorders.

EVALUATION OF THE STATE OF THE CUTANEOUS CIRCULATION

INSPECTION AND PALPATION

Nutritional Disturbances: Valuable information regarding the circulation through the skin and subcutaneous tissue can be obtained merely by inspection and palpation of the extremities. For example, healed, depressed scars on the fingers (Fig. 1A) or toes, loss of portions of digits (Fig. 1B), or the presence of large, healed or open ulcers (Figs. 1C and 1D) should make one suspect the existence of a definite impairment of cutaneous blood flow. However, before reaching this conclusion, it is necessary to rule out such etiologic factors as venous or lymphatic stasis, trauma or burns in a limb with normal blood flow and various types of systemic conditions associated with the production of ulcers and gangrene in the extremities.

Of significance also are the texture and consistency of the skin and subcutaneous tissue. As a rule, firmness and good elasticity of these structures suggest adequate nutrition, while areas of softness, dimpling (Fig 2A) or flabbiness may indicate an impaired blood supply. The absence of wrinkling of the skin over the joints of the fingers may be due to abnormal attachment of this structure to the subcutaneous tissue, as in scleroderma (Fig. 2B). Other abnormal findings are thickening of the tips of the fingers and piling up of scaly material at the junction of the nail plate and the fleshy portion of the digit (Fig. 2C).

Alterations in Skin Temperature: Palpation of the limbs in order to determine temperature of the skin may give definite information concerning changes in cutaneous circulation. However, in evaluating the alterations, it is necessary to consider the period elapsing between the time the patient came in from outdoors and examination of the extremities. Obviously, during the winter months even the normal limb will remain cold for some time after the patient has entered the office. Therefore, one cannot draw any definite conclusions from such a finding unless low temperature of the skin persists.

Alterations in Nail Structure: Of further importance in regard to the efficiency of the cutaneous circulation is the state of the toe nails. In the presence of an impaired local blood flow, either as a result of permanent organic changes in the vessels or of vasospasm, these structures will manifest certain abnormalities, such as deformity, brittleness and pigmentation. In occlusive arterial vascular disorders there may also be an increase in thickness of the nail substance and parallel ridging. At the same time a history is usually elicited of slow growth of the nails. In vasospastic conditions, such as Raynaud's disease and post-trench foot syndrome, the most frequent abnormality is thinning of the proximal nail folds, with gradual merging into a widened cuticle.

Growth of Hair: As in the case of the nails, the growth of hair on the toes is related to the state of nutrition of the cutaneous and subcutaneous tissues. In the limb with a markedly

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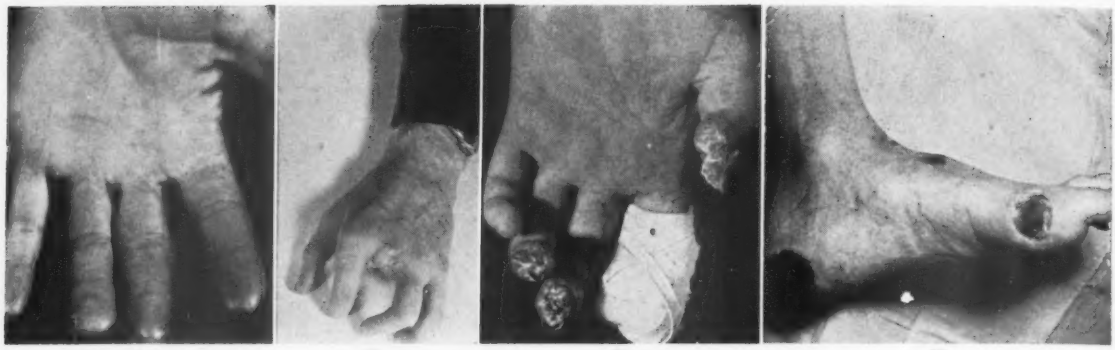


A B C D

FIG. 1. *Signs of impaired arterial circulation.* A, depressed scar on third finger following healing of an ulcer due to Raynaud's disease. B, amputation of third finger for gangrene due to thromboangiitis obliterans. C, ulcerations of fingers due to thromboangiitis obliterans. D, ulcerations covered with eschars, due to arteriosclerosis obliterans.

impaired circulation, growth of hair may stop entirely. However, in the presence of mild or moderate ischemia, it may still be normal. The presence of hair on involved toes may at times delay amputation of a limb, on the possibility that spontaneous healing of the nutritional disturbance might still take place.

POSTURAL COLOR CHANGE

Considerable information of value may be obtained from a study of skin color of the extremities in different positions. For this type of examination it is essential to have a good light, preferably from a natural source.

Horizontal Position: With the patient lying on an examining table, the toes should normally demonstrate a slight flush. Pallor, cyanosis and rubor generally indicate the presence of some alteration of the local vascular system, especially when the response is limited to one limb or one or more digits. However, it is necessary to point out that changes in skin color are significant only if one can eliminate such systemic conditions as congestive heart disease, a pneumonic process interfering with oxygenation of the blood, blood dyscrasias, carbon monoxide poisoning and shock.

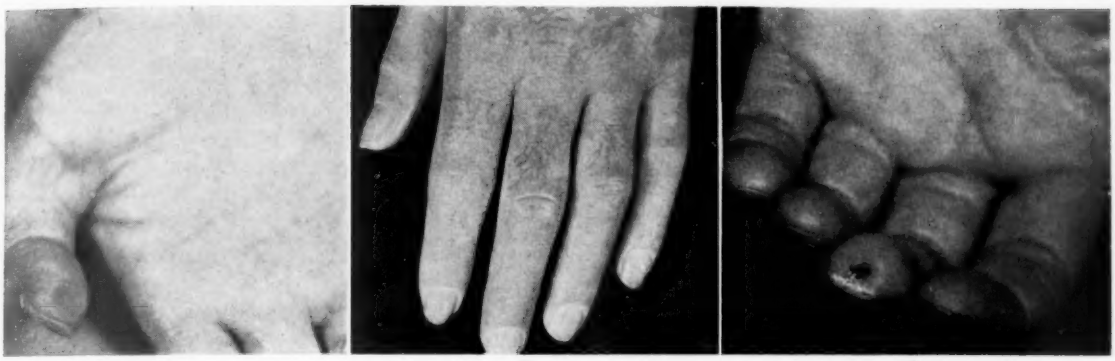
Elevated Position: With the lower extremities in the elevated position, the skin of the feet should continue to remain pink. The appearance of pallor in the distal portion of the limb is good evidence that reduced arterial circulation exists. If no change occurs, it is necessary to have the patient dorsiflex his feet repeatedly at the ankles, while maintaining them in the elevated position, and then their ventral surfaces are observed and compared. This added maneuver may now bring out a pallor of the toes or of adjoining portions of the feet. Such a change is considered to be a positive plantar pallor test (Samuels' test).

Dependent Position: After the extremity has been elevated for some time, it is placed in the dependent position and the changes in color are observed. Normally a pink color will appear in ten seconds or less (time of return of color in dependency). In a patient with arterial impairment, however, there is a delay in the reappearance of the skin color to as long as forty-five to sixty seconds or more, the change being irregular and patchy rather than uniform. In the presence of varicosities the test is of little value, since skin color will return almost immediately after the feet are placed in dependency. This is due to the retrograde flow of blood into the subpapillary venous plexuses from proximal veins with incompetent valves.

Changes in skin color occurring when the extremity remains in dependency are also of value in determining the state of the cutaneous circulation. In the presence of impaired local blood flow, intense cyanotic rubor may develop slowly in the foot. This type of response is generally observed in the limb which manifests delay in return of color when first placed in dependency. The appearance of rapid cyanosis with a change to this position indicates that the tone of the superficial vessels is low or absent and that immediate pooling of blood is taking place in them. Slowly forming mild cyanosis, without rubor, does not have much significance and, in fact, may be a normal response.

SUBPAPILLARY VENOUS PLEXUS FILLING TIME

A simple test to determine the state of tone



A B C

FIG. 2. *Changes in skin and subcutaneous tissues*, on the basis of an impaired arterial circulation. A, dimpling of skin in Raynaud's disease, due to loss of subcutaneous tissue. B, loss of normal wrinkling of skin over distal joints in scleroderma, as a result of binding down of skin to subcutaneous tissue. (From ABRAMSON, D. I. Diagnosis and Treatment of Peripheral Vascular Disorders. New York, 1955, Paul B. Hoeber.) C, piling up of scaly material at junction of nail plate and fleshy portion of digit in Raynaud's disease. A small ulcer at tip of finger is also present.

of the small cutaneous vessels consists of applying firm digital pressure to the skin for several seconds and then studying the color changes produced by sudden removal of the finger. Normally, the procedure causes pallor of the skin, as a result of displacement of blood from the subpapillary venous plexus locally into the surrounding and deeper tissues, followed by a return of normal color within a second or two. A delay in the response (four to five seconds) may be noted in the presence of decreased arterial inflow resulting from either excessive vasospasm or structural changes in the vessels. If such a change persists after removal of vasomotor tonus, then it must be due to organic arterial disease or to paralysis of the subpapillary venous plexus.

The subpapillary venous plexus filling time not only gives considerable information regarding the turgor of the skin, but may also help differentiate between living and non-living tissues. Application of pressure to an apparently cyanotic area with no appearance of transient pallor indicates that an irreversible change has occurred and that superficial or deep gangrene will ultimately develop in the involved site.

HISTAMINE WHEAL TEST

The intracutaneous administration of a dilute solution of histamine may also be of value in assessing the state of the cutaneous circulation. It gives pertinent information regarding the rate of progression of an occlusive arterial vascular disease, and it may be helpful in preventing useless surgery and in determining the proper level of amputation of an extremity.

In order to carry out the test, the limb is placed in the horizontal position and about 0.1 cc. of a 1:1000 solution of histamine acid phosphate is injected intracutaneously or pricked into the skin with a hypodermic needle at different levels: the dorsum of the foot, the leg below the knee and the thigh just above the knee. The sites are then examined either visually or by palpation for the appearance of a wheal. A delay in the production of this change beyond the normal range of from three to five minutes is interpreted as indicating definite impairment of the circulation. In the absence of wheal formation, the blood supply can be considered to be precarious. There are various gradations in the magnitude of the reaction, and these can be tabulated as an absent, faint, fair or marked response.

It must be borne in mind that the histamine wheal test is only of value in determining the state of the cutaneous circulation. A normal response does not rule out the possibility of severe occlusive disease of the arteries in the muscle, the converse also being true. In addition, the procedure does not differentiate a reduced cutaneous blood supply due to excessive vasospasm from that following structural changes in the blood vessels.

DETERMINATION OF DEGREE OF INVOLVEMENT OF MAIN ARTERIES

EXAMINATION OF PERIPHERAL PULSATIONS

One of the most important steps in a vascular examination is palpation of the main arteries

in the extremities to determine the state of their pulsations. Every vessel that can be examined should be checked, even though the changes appear to be limited to one limb.

Systemic Disorders and Extrinsic Factors Affecting Pulsations: It is necessary to point out that there are states other than local changes in the blood vessel which alter the amplitude of the peripheral pulsations. Among these are systemic disorders affecting the heart and circulation, syndromes producing obstruction of the great vessels proximal to the extremities and local abnormalities of non-vascular tissues (edema, induration and brawniness of skin, and deposition of large amounts of subcutaneous fat). Among the systemic conditions producing alterations in peripheral pulsations are shock, atrial fibrillation, the terminal stage of congestive heart failure, aortic stenosis, constrictive pericarditis, pericardial effusion with tamponade and myocarditis. Changes in the pulsations of the lower extremities may be produced by such disorders of the aorta as thrombosis at its bifurcation and dissecting aneurysm. Extrinsic pressure on this vessel or its main branches by tumors or other structures will produce a similar type of change.

Conditions Producing Local Changes in Arteries: If the various aforementioned conditions can be ruled out, then variations in the amplitude, or complete absence, of peripheral pulsations can be attributed to local changes in the arteries, consisting of either structural alterations or temporary vasospasm or vasodilatation. The most frequent causes of permanent abnormalities of the vessel wall are arteriosclerosis obliterans and thromboangiitis obliterans. Mönckeberg sclerosis, in which there is a deposition of calcium in the media, may also produce some damping of the pulse wave. An increase in vasomotor tonus may be noted in such conditions as Raynaud's disease or Raynaud's phenomenon, acrocyanosis, causalgia and post-traumatic vasomotor disorders. A decrease in normal vasomotor tonus, producing bounding pulses, is seen in erythromelalgia and in the early stage of immersion foot and frostbite.

Technic of Examination: In the examination of the peripheral pulses, it is necessary to compare the amplitude and force of pulsations in one artery with those in the corresponding vessel on the opposite side. Only with experience can one determine what is a normal pulsation for any single artery. The observer should be comfortable while examining for pulsations, for otherwise he may be unsuccessful in palpating an artery merely because he assumes a position which places a strain on the muscles of his body, with a resultant dulling of his pereptive senses. It must also be kept in mind that when firm pressure is utilized in feeling for the vessel, the pulse in the finger of the examiner may be mistaken for the one in the artery of the patient. This can be readily differentiated by having the observer count the beats aloud, while another checks the rate and rhythm against a different pulse in the patient, preferably the corresponding vessel on the opposite extremity. Another precaution to be taken is to vary the pressure depending upon the depth of the vessel below the skin. This step is also important in the presence of weak pulsations, which may not be felt if the examining fingers are applied to the skin with much force.

Upper Extremities. In the upper extremities the *brachial artery* can be readily palpated by encircling the arm in its lower third with the examining hand and compressing the tissues on the medial aspect against the humerus (Fig. 3A). The *radial artery* is felt in the usual manner on the ventral surface of the wrist, medial to the styloid process of the radius. If pulsations are not palpated in this site, it is advisable to continue the examination proximally until the artery is palpated. Such a situation may exist if the vessel is occluded in its distal portion.

The *ulnar artery* can be felt at the same level at the wrist as the radial artery except that it is on the opposite side. (Fig. 3B). Generally it is just as readily palpable as the latter. At times, however, it can only be felt with difficulty or not at all because of an aberrant location. Under such circumstances, it is necessary to perform the ulnar confirmatory test before concluding that the vessel is absent. The extremity is elevated, in order to facilitate venous drainage, and the radial artery is obliterated by the use of firm digital pressure. The subject then opens and closes his fist a number of times to effect further venous outflow, and, with the compression of the radial artery still maintained, the hand is brought down to the level of the heart and the fist is opened, no attempt being made to extend the fingers fully. If the ulnar artery is intact, there will be immediate flushing of the palm as blood enters the cutaneous vessels from the

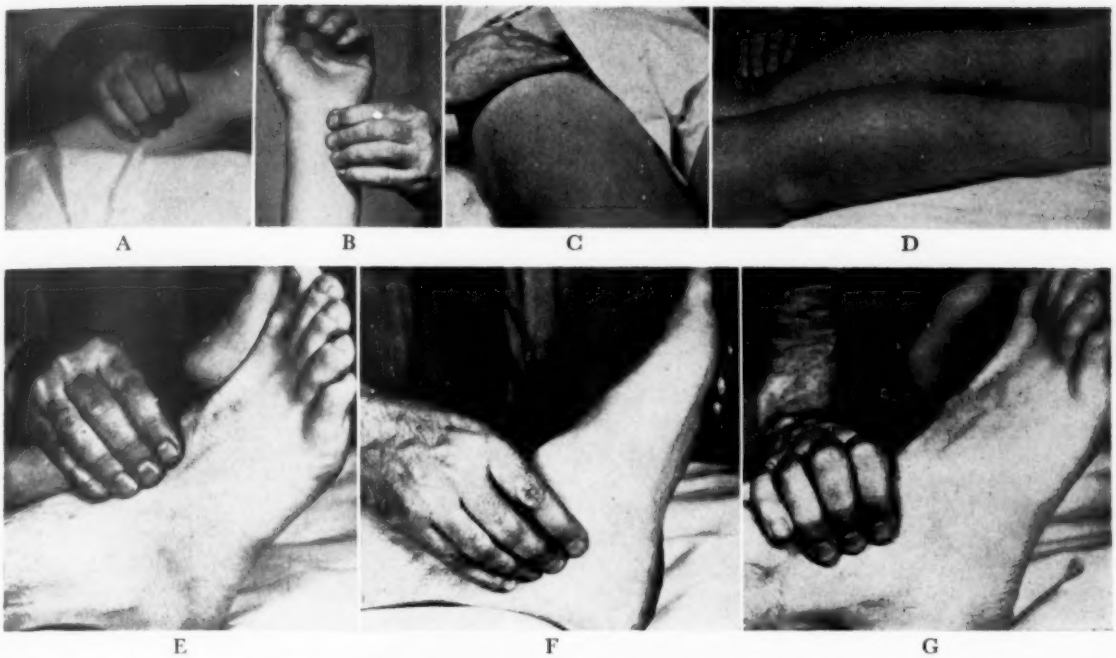


FIG. 3. *Technic used in palpation of peripheral arteries.* A, brachial artery. B, ulnar artery. C, femoral artery. D, popliteal artery. E, dorsalis pedis. F, posterior tibial artery. G, perforating branch of peroneal artery. (From ABRAMSON, D. I. Practical procedures in bedside diagnosis of peripheral vascular disorders. *GP*, 6: 546, 1955.)

ulnar artery and the superficial volar arch. If the skin remains blanched as long as pressure is applied over the radial artery, to become flushed when this is removed, it may then be assumed that either the ulnar artery is obliterated by a disease process or some type of anatomic anomaly exists in the connection between this vessel and the volar arches.

Lower Extremities. Examination of the arteries of the lower extremities, with the possible exception of the popliteal, is accomplished without much difficulty. The *femoral artery* can be readily felt in the groin below Poupart's ligament (Fig. 3C), its pulsations normally being greater than those of any other vessel in either the upper or lower extremities.

Because the *popliteal artery* is generally located quite deeply in the fatty tissues of the popliteal fossa, its palpation presents somewhat of a problem. A satisfactory procedure consists of having the patient lie prone with the foot of the extremity being investigated crossed over the back of the opposite limb, thus relaxing the tissues traversing the popliteal space. Considerable digital pressure is required to feel the artery, and this can be obtained by placing the fingers of the other hand over the examining fingers and pressing firmly (Fig. 3D). In such a manner the perceptive sense of the palpating digits is not dulled, as would occur if these were performing the dual function of exerting force to compress the tissues and of seeking the vessel.

The *dorsalis pedis artery* is usually felt in its course over the dorsum of the foot and occassionally it may be seen to pulsate. Its position with respect to the bones of the foot, however, is quite variable. In most instances it lies somewhat medial to the midline (Fig. 3E). The entire dorsum of the foot should be examined before deciding that the vessel is not present.

The *posterior tibial artery* can be felt as it passes behind and beneath the medial malleolus. In the case of the left foot, the examiner stands to the left of the patient and cups the fingers of his right hand over the medial malleolus, so that the finger tips slide off to enter the groove below (Fig. 3F). In the case of the right foot the opposite position and the left hand of the examiner are utilized. Generally, firm pressure is necessary to feel the artery, the procedure being facilitated by simultaneously dorsiflexing the foot slightly with the other hand, so as to put the vessel somewhat on a stretch (Fig. 3F).

In all instances search should be made for the presence of *anomalous arteries*. For example, with obstruction of the popliteal artery, the lateral or medial superior genicular arteries may become prominent in their course over the knee. At times, in the absence of the posterior tibial artery, a large vessel may be present along the upper border of the lateral malleolus which is an enlarged perforating branch of the peroneal artery (Fig. 3G).

Interpretation of Results: Absence of pulsations in the main arteries of the extremities does not always have the same connotation. Generally, inability to palpate the brachial, radial, ulnar, femoral or posterior tibial arteries indicates existence of either occlusive arterial vascular disease or marked vasospasm. On occasion, however, the posterior tibial artery may be present but impalpable behind a prominent medial malleolus, found in patients with squat feet. Similarly, the popliteal artery may not be felt because of anatomic alterations in the popliteal fossa. The absence of one or both dorsalis pedis arteries has been reported as a normal variant in approximately 13 per cent of people. When it cannot be felt, it is advisable to palpate anteriorly over the ankle joint for the anterior tibial artery, of which it is a continuation.

OSCILLOMETRY

Considerable difference of opinion exists regarding the value of oscillometry in peripheral vascular disorders. Some workers believe that the test is of little use, while others consider it an important part of the vascular examination. On the basis of personal experience and observation, it would appear that the latter opinion has much in its favor.

The oscillometer consists of a sensitive aneroid which is connected to a modified pneumatic cuff. The pulsatile variations in size of limb with each cardiac systole produce corresponding alterations in the air volume of the cuff. These are transmitted to the aneroid where they cause an amplified swing of the recording needle, the range of movement being noted on an arbitrary degree scale of the instrument. Since the increase in volume of the limb is due to the fact that initially blood is entering the main arteries more rapidly than it can escape into the capillary bed, the magnitude of this response, as recorded by the oscillometer, is therefore an indirect index of the rate of local arterial inflow.

Technic: The pneumatic cuff is wrapped snugly around the limb, inflated to above systolic blood pressure, and the pressure is lowered in steps of approximately 10 mm. Hg by means of an escape valve. Following each drop, the cuff is connected with the recording capsule and the range of movement of the needle is noted. The important reading is the one indicating the greatest excursion of the needle, the height of pressure at which this occurs appearing to have little significance.

In each case the cuff is applied around either two or three sites. In the upper extremities readings are usually obtained at the upper part of the forearm and at the wrist. If a reduction is observed at the higher level, then the cuff is also applied to the lower part of the arm. In the lower extremities the routine sites of application are the calf and the lower part of the leg above the ankle. If the results from the former location are below normal, determinations are then made at the thigh just above the knee. Placing the cuff around the hand or foot gives information of little value, since the bony structures may support it and so interfere with the transmission of the pulsations to the instrument.

Normally there is a considerable variation in the results obtained from the different sites. The range is between 5 and 12 units or higher for the arm above the elbow, the upper part of the forearm, the calf and the thigh just above the knee, and between 1.5 and 4 units or higher for the wrist and the leg immediately above the ankle. Figures which fall below the lower limit for any one site should be viewed with suspicion. At times in the obese individual the results at the thigh may be less than those at the calf, which obviously is an artifact.

Interpretation of Results: Oscillometry is an important tool in the evaluation of the peripheral arterial vascular status of a patient, provided that one is fully aware of its limitations. It not only substantiates the information obtained by palpation of peripheral pulses, but it also gives a much more complete picture of the state of the main arteries than can possibly be obtained from digital examination alone. With it a readily reproducible record is available, which is expressed quantitatively, in contrast to the purely qualitative and subjective impression that results from palpation of an artery.

Repeated studies at intervals will ascertain whether or not there has been any progression in the obliterative process. The procedure

is also of value in determining mild degrees of impairment of arterial circulation, not reflected in sufficient reduction in amplitude of pulsations to be obvious by palpation. Similarly, it is helpful in diagnosing the presence of a block in an artery and its location, information which is very important when embolectomy is being contemplated for the treatment of an occlusion of a critical vessel by an embolus. Finally, the procedure is helpful when local changes in non-vascular tissues make palpation of vessels difficult, as in the presence of obesity, edema and induration and thickening of the skin around the ankle.

Limitations of Method: A limitation of oscillometry is the fact that the instruments available for clinical use are not sensitive enough to pick up oscillations in small collateral vessels, in which the pressure is lower than in the main arteries of a limb. Since in an occlusive arterial vascular disease, this secondary system frequently carries on the principal function of supplying the tissues with nutrition, it is obvious that information derived from oscillometry alone would be of little value in determining the over-all state of the local circulation. Conversely, there could be structural impairment of the small arteries and arterioles distal to the main channels, leading to partial anoxia of the tissues, and still with no corresponding decrease in the oscillometric measurements of the limb. Because of these inherent weaknesses of the method, oscillometry is of little value in arriving at a proper conclusion regarding prognosis.

VENOUS FILLING TIME

The rapidity with which the superficial veins of a lower extremity fill after having been collapsed gives pertinent information concerning the rate of local arterial inflow. To perform the test, the limb is first raised for several minutes to drain the blood out of the cutaneous vessels, and then quickly lowered. The period required for the superficial veins on the dorsum of the foot to become visible is recorded, a normal response occurring within ten seconds after the limb is placed in dependency (venous filling time). Delays beyond this time indicate some arterial impairment; however, the test does not differentiate between functional and organic disorders unless it is repeated after removal of vasomotor tone. It is also necessary to point out that if varicosities exist, in which case the superficial vessels fill immediately with blood coming from proximal veins, or if the veins on the dorsum of the foot cannot collapse when emptied of blood because of fibrous changes in their wall, the results of the procedure are of no value.

DETERMINATION OF DEGREE OF VASOSPASM

Since a reduction in local circulation due to vasospasm is much more amenable to treatment than that resulting from permanent structural changes in the wall of an artery, it becomes of paramount importance to determine to what degree this state exists in the patient with a peripheral vascular disorder. Such information can be obtained by determining the elevation in cutaneous temperature produced by temporary inhibition of sympathetic control. The assumption is made that the magnitude of the resulting change is a reflection of the increase in cutaneous blood flow which follows passive dilatation, due to removal of either normal or exaggerated vasomotor tone.

Technic: In order to obtain dependable readings of skin temperature, it is necessary to have the patient exposed to constant environmental conditions, with drafts eliminated. However, there is no need for a temperature-regulated room in order to carry out the procedure. Although a sensitive galvanometer for the determination of the rise in skin temperature is preferable, for clinical purposes the use of a modified mercury thermometer with a flat, widened base is adequate.

Control cutaneous temperature readings are collected after the patient is at bed rest for twenty minutes, during which time the extremities to be studied are exposed to room air to permit equilibrium to take place with the environmental temperature. All external stimuli are reduced to a minimum. The control measurements are obtained from the digits and from several locations on the dorsum of hand or foot and on the ventral surface of the forearm or leg.

Vasomotor tone can be removed by means of a number of different procedures. Among these are procaine block of peripheral nerves, blocking of sympathetic ganglia or trunk and reflex or indirect vasodilatation. In the lower extremity, partial sympathetic denervation of toes is obtained through anesthetization of the posterior tibial nerve with 1 per cent procaine solution. In the upper extremity, the desired effect is produced by anesthetization of the ulnar nerve at the elbow and the median

nerve at the wrist. When both structures have been properly blocked, inhibition of vasomotor tone will be noted in all fingers. Blocking of sympathetic ganglia or trunks can be produced by depositing procaine around the appropriate paravertebral sympathetic ganglia or into the spinal canal to produce anesthesia of the nerves arising from the spinal cord. Indirect vasodilatation is produced by applying heat to various parts of the body, excluding the limbs under study.

Interpretation of Results: After removal of sympathetic control by any one of the methods already mentioned, the readings in the hands and feet of normal persons should rise to at least 86°F. and generally to between 88° and 95°F. In the patient with excessive sympathetic activity, inhibition of vasomotor tone will cause a change from low control readings to 88° to 95°F., results which are similar to those obtained in normal subjects. However, the magnitude of the increase is much greater since the control figures are lower. In the patient with obliterative vascular disease alone, removal of vasomotor tone generally results in a rise from around 75° or 77°F. to 80° or 82°F. but not higher. In other words, despite elimination of all sympathetic tone, the normal increase in arterial inflow does not occur because structural changes in the cutaneous vessels prevent adequate vasodilatation.

The various tests which temporarily remove sympathetic control over blood vessels in the extremities are therefore of value in differentiating a primarily occlusive arterial vascular disease from one in which increased vasomotor tonus is solely or chiefly responsible for a reduced local blood flow. Since these procedures also give information concerning the capacity of the vascular bed to dilate, they are useful in arriving at a decision as to whether or not a procedure such as sympathectomy is indicated as a therapeutic measure. On the other hand, they are of no help in assessing the state of the muscle circulation.

Summary and Conclusions

An evaluation of the arterial circulation in the extremities can be readily obtained through the use of several types of clinical tests requiring no elaborate apparatus or special skills. These have for their primary purpose either the assessment of the state of the cutaneous circulation, the determination of the amount of impairment of blood flow through the main arterial channels or the measurement of the degree of existing vasomotor tonus. To obtain a comprehensive survey, it is necessary to utilize all three groups, since the results from one alone might be inadequate for this purpose or might even be misleading.

Some Observations and Questions on the Medical Management of Intermittent Claudication*

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IN CONTRAST to surgical management of intermittent claudication when the arterial occlusive lesion can actually be removed or circumvented by grafting, medical management offers nothing "specific."[1-3] Since such surgery is often impossible, undesirable or unsuccessful,[4,5] we are usually compelled to resort to medical management for this obstinate symptom. In an effort to improve the medical management of intermittent claudication we have been studying its natural history, raising some questions as to its pathologic physiology and testing some of the drugs reported as being helpful in its treatment.

NATURAL HISTORY

Relatively little has been written on this subject.[5-10] Horwitz and I,[5,14] therefore, have been following the course of intermittent claudication in the lower extremities resulting from arteriosclerosis obliterans in patients receiving no treatment, other than the usual prophylactic foot care for peripheral arterial disease and occasional cutaneous vasodilators (Priscoline®, whiskey). No drugs or surgery reported as beneficial for intermittent claudication have been used. To determine the change in claudication distance, we have been relying primarily on one of the standard claudication tests using a horizontal treadmill. When the patient is unable to coordinate on the treadmill, a "walking test" is used, the patient being allowed to walk at his usual pace on a level floor. With either test, he walks until stopped by his claudication, but not beyond a ten-minute time limit. These two tests were selected because the exercise involved resembles the exercise of ordinary walking. (Some other claudication tests are listed in Table I.) It should be borne in mind, however, that *no* test for claudication is objective, since the end point always depends upon production of a symptom—"pain," "tightness," "weakness" or "numbness"—in the affected extremity.

Our observations have brought out three points:[5,14] (1) *Intermittent claudication may remain of only symptomatic importance.* Our fifty-one patients had claudication for an average of over five years without loss of limb or livelihood from their peripheral arterial disease. The common belief that claudication is necessarily the harbinger of gangrene is therefore unfounded. (2) *Intermittent claudication often improves with time alone.* The walking distance of our patients, when first examined, averaged one and a half city blocks, but two years later it increased to an average of three and a half city blocks. Similar results were obtained with the treadmill tests; at the end of a year, half of our patients could walk a longer time than when originally tested. (3) *The response to claudication tests varies considerably* (*Table II*). The treadmill speeds necessary to produce claudication differed widely; over one-third of the patients reached the time limit of ten minutes without having to stop because of claudication, and almost one-fifth of the patients were compelled to stop before this time limit for reasons other than claudication. In some patients having arterial disease of both legs claudication developed in the opposite leg when a second claudication test was made on the same day.

Improvement in intermittent claudication is

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TABLE I
Some Tests of Intermittent Claudication

Type	Description	Advantages
Treadmill[6,7,11–14]	Walks in place; belt moves at set speed	Desired speeds easily reproduced
"Walking test"	Walks to and fro on level floor	Requires no equipment or training of subject; exercise identical to that of ordinary walking
Paced[1,15,16]	Accompanied by paced observer, usually at 120 steps/minute	
Non-paced[14]	Unaccompanied, and walks at his usual pace	
Toe-stand[16,17]	Contracts calf muscles while standing on toes	Does not require as large an area as does the walking test
Walking steps[18–20]	Usually up and down "Master steps"	Does not require as large an area as does the walking test
Bicycling[21]	Ordinary bicycling in place	Usually for vigorous testing
Foot pedals, pulleys[22–24]	Weights moved at a given distance and rate	Each leg can be tested individually
Passive exercise[25]	Calf muscles stimulated electrically and fatigue curve obtained	Most objective of claudication tests

TABLE II
Claudication Tests on Sixty-One Patients and Results

	No. of Tests
Type of Test	
Treadmill—average speed 141 ft./min. (85 to 271 ft./min.)	357
"Walking"—average speed 241 ft./min. (140 to 350 ft./min.)	67
Total	424
Results	
Stopped before ten-minute time limit:	
Claudication	201
Angina or dyspnea	26
Other causes (symptoms in legs other than claudication—technical failure, generalized tiredness, poor coordination on treadmill)	49
Reached time limit	148
Total	424

said to occur more frequently during the first year,[2–26] but our observations show no such pattern, improvement being noted at almost any time. There is also no rule concerning the patient's age; many of our patients who improved were over sixty years of age.

The prognosis of intermittent claudication, therefore, is unpredictable and not necessarily unfavorable.

Pathologic Physiology

The pathologic physiology of intermittent claudication is fairly well defined.[27] When the affected extremity is at rest, blood flow to the muscle is within normal limits. On exercise, however, the normal tenfold, or greater, increase is not obtained. Instead the local circulation will rise only two or threefold; this increase in flow appears relatively late and requires a longer than normal period to return to its pre-exercise value.[24,28–31]

We should like, however, to raise several questions: (1) *What is the cause of either the spontaneous decrease, or the spontaneous increase, in the severity of intermittent claudication?* With a change in the severity of claudication, there is usually no corresponding change in the physical appearance of the limb or in the results of the common circulation tests. Whether or not the change in claudication is due to an alteration in the patency of the major arteries, or to a change in the collat-

eral circulation, is unknown. Is it even possible for *improvement* in claudication to be brought about by a *worsening* of the circulation, a further decrease in circulation causing death of some partially viable muscle cells and rendering them completely insensitive to the effects of ischemia? Such improvement in claudication would be analogous to the occasional relief of angina pectoris that results from myocardial infarction.

(2) *Is Ratcliffe's classification of claudication valid?*[32] He classifies claudication into three types: (1) claudication disappearing with continued walking; (2) claudication remaining unchanged with continued walking and (3) claudication becoming more intense with continued walking, compelling the patient to stop. If categories (1) and (2) do exist, and we have encountered a few such instances, then we must reexamine our basic concept of the pathologic physiology of intermittent claudication—that the relative ischemia of the muscle becomes more and more pronounced with increasing exercise, eventually causing pain and the cessation of walking.

(3) *What exactly happens to the blood flow in the leg while the patient is walking?* Most of the measurements in the literature have been made either in the recumbent subject immediately after walking or while a single leg is being exercised.[24,30,31] In the former instance, the changes in calf blood flow during exertion are not being measured. In the latter instance, unlike that in the clinical situation, there is little redistribution of arterial blood flow throughout the rest of the body [33,34] (Fig. 1).

To understand fully the relationship between local circulation and intermittent claudication, blood flow in the calf should be measured while the subject walks, as well as in the postexercise period. Furthermore, blood flow should be "fractionated" to determine what percentage is flowing through skin and what percentage through muscle and, if possible, in what portion of the muscle. It would also be of value to ascertain the amount of blood passing through the usual channels (arterioles, capillaries and venules) and the amount traversing the arteriovenous anastomoses, since the availability of nutrients to the tissues from these two types of blood flow probably differ. Such measurements, however, are probably impossible with existing methods.

(4) *What metabolic changes take place in the ischemic muscle?* Relatively few experiments have been carried out on this aspect of claudication.

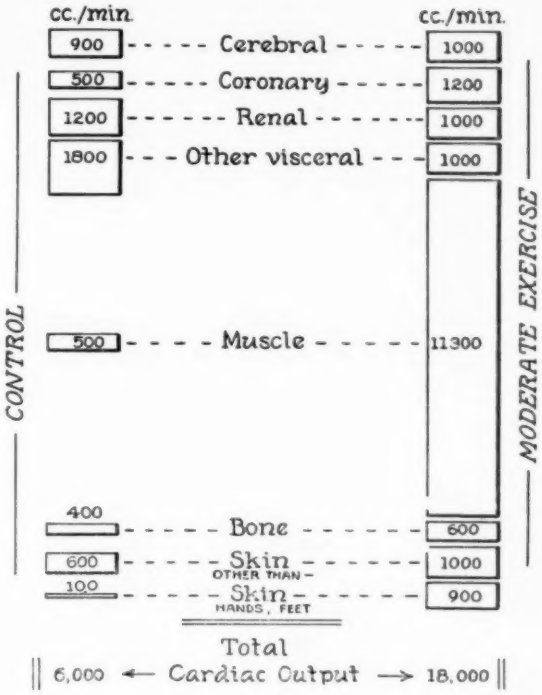

FIG. 1. Effect of moderate exercise (brisk walking) upon arterial blood flow distribution in the normal subject (Courtesy of Dr. Orville Horwitz[33]).

Some authors suggest that a "P" factor, possibly related to the lactates, accumulates and causes claudication[35,36] but others question this.[37] Some believe that hypoxia also plays a role.[38,39] Only a few studies have been made on the electrolytic changes in the exercising muscle.[40]

(5) *Does the occurrence of intermittent claudication always entail an afferent nervous component?* Some patients complain of "weakness" in the extremity, rather than "pain." Perhaps "weakness" is simply a manifestation of a "primary" muscle cell failure and, unlike "pain," needs no afferent stimulus to the central nervous system.

Medical Management

Realizing that intermittent claudication can improve significantly with time alone, that certain aspects of its pathologic physiology have not been settled and that the blood vessels of exercising muscle may already be fully dilated, we undertook the evaluation of some drugs reported beneficial to intermittent claudication.

Intra-arterial Histamine: At the outset, we wished to confirm the report that the injection of histamine into the femoral artery of the affected limb was regularly followed by relief of claudica-

TABLE III

Intra-arterial Injections of Histamine for Intermittent Claudication in Five Patients[42]

Patient	Histamine Injections		Follow-up	
	No.	Date	Date	Results
G.R.	9	Mar.–May 1955	Oct. 1955	Temporarily improved
	1	Oct. 1955	Nov. 1955	Temporarily improved
G.O.	3	June 1955	Nov. 1955	Temporarily improved
	6	Jan. 1956	Jan. 1956	Not improved
B.U.	3	Dec. 1955	Jan. 1956	Not improved
E.L.	2	Sept. 1955	Oct. 1955	Not improved
H.A.	1	Aug. 1955	Sept. 1955	Not improved

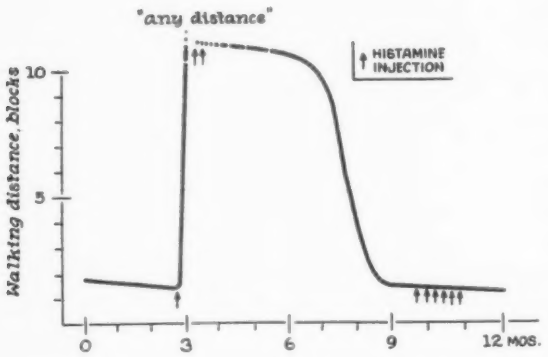

FIG. 2. Effect of intra-arterial histamine injections on intermittent claudication (see Table III, patient G. O.).

tion, an improvement attributed to the development of collateral blood vessels in the limb.[41]

We have given a total of twenty-five such injections to five patients selected because they had a "stable" degree of claudication[42] (Table III). Two of the four patients receiving three or more injections stated that they could walk farther after the injections. One of these patients could walk "any distance" after his first series of injections, but was not helped by a second series (Fig. 2).

Our experience with intra-arterial administration of histamine is inconclusive, but we did get the impression that it is of some value. Its value should be further explored, especially since a placebo injection of physiologic saline,[43]

TABLE IV

Some Treatment Reported as Favorable for Intermittent Claudication

Site of Action	Therapy	Possible Mode of Action
Heart	Arlidin[46]	Increases cardiac output
Artery	Low-fat diet[47]	Controls atherosclerosis
	Anti-atherogenic drugs[19,20]	
	Arterial grafting[4,5]	Removes or circumvents occlusion
Arterioles	Nicotinic acid[49]	Dilates arterioles; promotes development of collateral circulation
	Arlidin[16,44,45,48]	
	Histamine[12,13,41–43]	
	Papaverine[50]	
	Aminophyllin[51]	
	Sympathetic nerve block[52]	
	Sympathectomy[9]	
	"Walk to limit"[2,53]	
Skeletal muscle	Slower walking pace[54]	Decreases demands for blood
	Pancreatic extracts[1,15,27]	Improves muscle metabolism
	Alkali administration[55]	Counteracts local acidosis in tissues
	Procaine injection of muscle[17,56]	Relieves "local spasm"

or of certain vasodilating drugs,[12] into the femoral artery has not produced the same results as has histamine. If histamine helps claudication, the question of what physiologic process may be involved is thought-provoking, for it cannot be explained by the known, very transient, dilating effect of histamine.

Arlidin®: Another promising vasodilator is Arlidin, improvement in claudication being reported after several weeks of its oral administration. It belongs to the epinephrine group and, like epinephrine, increases the blood flow in the resting muscle of the limb. Unlike epinephrine, however, it can be given orally and does not constrict the digital blood vessels.[16,44,45] We realize again, that such a drug would be expected to have little or no value if the circulation of the claudicating muscle is already fully dilated, unless possibly by increasing cardiac output[46] or by promoting the growth of the collateral circulation.

We have been studying the effects of a single oral or subcutaneous dose of Arlidin in a small group of patients. Intermittent claudication tested soon after administration of the drug has not been consistently improved, but some of the patients remarked that their daily walking distance has been.

Other Modes of Therapy: A wide variety of therapies has been reported in the literature as beneficial for intermittent claudication. Some of these, their sites of action and possible modes of action are listed in Table IV. In some instances, the physiologic basis is apparent, the improvement in walking distance has been measured by claudication tests, and the "double-blind" method has been used. In other instances, the physiologic basis is obscure, and improvement in claudication is based solely upon the patient's own evaluation of his daily walking distance.

Finally, medical management of intermittent claudication still offers nothing specific, but any promising therapy is worthy of a trial when claudication is severe. We must bear in mind that useful therapy for claudication need not be curative; if a patient's walking distance can be increased to the point where he can carry out most of his daily activities, his handicap is slight.

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Deep Venous Thrombosis and Pulmonary Embolism

Prediction, Prevention and Treatment*

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NEITHER the frequency nor the importance of the debilitating and fatal consequences of thromboembolic disease has been fully appreciated by most physicians. The following data are presented to stress the high frequency of this disease, the serious and important nature of its associated sequelae and the difficulties encountered in making the clinical diagnosis. Deep venous thrombosis and pulmonary embolism are disorders of major significance and are responsible for much long term disability and an appreciable mortality. If there is to be a real reduction in the incidence of pulmonary embolism and the postphlebitic syndrome of edema, induration and ulceration, there must be a greater awareness on the part of the clinician of the many and varied manifestations of thromboembolism, of the value of prompt and effective treatment and of procedures for prevention.

Extrapolation of data obtained at our hospital to mortality statistics of the United States suggests that there may be as many as 47,000 deaths annually in the United States in which pulmonary embolism is the sole cause; in addition, there may be three times this many deaths in which pulmonary embolism has at least played a significant role in the outcome.

There are no good mass surveys on the incidence of ulcers of the leg among the population of the United States. Boyd et al.[1] suggest that in England it is about five per thousand population. If this figure can be applied to our population, there may be as many as 850,000 people in the United States with ulceration of the leg, the majority secondary to postphlebitic change. The incidence of the other manifestations of the postphlebitic syndrome must be considerably higher than this.

A number of studies have shown that prompt diagnosis and adequate treatment of deep venous thrombosis can appreciably lower the incidence of embolic mortality and the significant disability associated with postphlebitic sequelae. Particularly with regard to pulmonary embolism, there is a real need to achieve a much higher diagnostic rate if one hopes to lower significantly the mortality rate from this complication. A review of the records of large autopsy series at our hospital[2] has shown that in only 10.6 per cent of patients with proved pulmonary emboli was a clinical diagnosis of venous thrombosis made prior to death. In another 8.6 per cent of these patients localizing signs, which should have resulted in a diagnosis of deep venous thrombosis of the leg, were present. The difficulties in diagnosis of this entity are illustrated by the fact that in the remaining patients (80.8 per cent) there were no signs or symptoms suggesting any thrombotic process in the veins of the leg, despite the fact that a maximum of less than 10 per cent of all emboli could have arisen from a cardiac source.

The repeated demonstration of a high failure rate in the clinical diagnosis of thromboembolic disease precludes the presentation of accurate figures on the incidence of this disease in a hospital population. Estimates based on the constant but rather low clinical diagnosis rate as proved at autopsy, plus prior figures obtained in clinically diagnosed cases of thromboembolism at our hospital, suggest that as many as 6 per cent of hospitalized patients have deep venous thrombosis, largely undiagnosed, during

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their hospital stay. (This is admittedly only a gross estimate; it is based on reasonably accurate data obtained from autopsy records, the percentage of cases diagnosed clinically, ratios between the incidence of deep venous thrombosis and fatal embolism, etc. However, this figure has been derived by several different technics, and the approximate incidence of 6 per cent has been obtained in each instance.)

Clinical Manifestations of Thromboembolic Disease

Deep Venous Thrombosis: We strongly believe that there is no justification for the clinical differentiation of the aseptic form of deep venous thrombosis into "phlebothrombosis" and "thrombophlebitis." These terms, in our opinion, represent different phases of the same disease. Organization of a thrombus in any vessel is associated with a sterile inflammatory reaction and round cell infiltration. The manifestations attributed to "thrombophlebitis" merely represent an advanced stage of a thrombotic process which is sufficiently extensive and severe so that deep-lying pathologic changes are reflected in superficial signs. Our studies have shown that it is fallacious to maintain that patients with "thrombophlebitis" are secure from pulmonary embolism; pulmonary emboli develop in a number of patients with the classic signs of thrombophlebitis. Although certain portions of a thrombus may be firmly attached to the vein wall, the propagating proximal tail of the thrombus is usually "free floating" and may easily fragment and result in pulmonary embolism. In addition, there is no histologic basis for distinguishing these entities. We have sectioned a number of thrombosed veins; one area will demonstrate round cell infiltration of the vein wall (supposedly characteristic of thrombophlebitis) while another section through the same thrombus a few millimeters away will show no sign of sterile inflammatory change in the vein wall.

Unfortunately, the majority of episodes of deep venous thrombosis are not associated with any signs or symptoms. All too frequently the first indication of venous thrombosis of the leg is the sudden death of the patient from fatal pulmonary embolism. In our series, even though the presence of iliac or caval thrombi was proved at autopsy, only half the patients had associated clinical signs, and many of these demonstrated only minimal unilateral edema. Complete but localized occlusion of the iliac vein will not produce edema if there is an adequate number of collateral channels for the return of venous blood. It is only when there is occlusion of many collateral channels as well that edema is present.

The signs and symptoms of deep venous thrombosis may be vague or totally non-existent. Rarely, plantar or calf pain will be present. It is usually dull and aching in character, but occasionally, patients will complain of true cramps in the calf of the leg. When pain is present, there is frequently an associated tenderness along some portion of the course of the deep venous system, in the plantar region of the foot, between the bellies of the gastrocnemius, in the popliteal area, along the femoral canal or in the lower part of the abdomen over the course of the iliac veins. Local heat and redness may be noted in rare instances. Fever and tachycardia may be suggestive findings, but frequently these manifestations may be explained away as due to other causes. In the usual case, even if present, these signs are of little diagnostic value.

Much more frequently, the only clinical sign suggesting the presence of a thrombus occluding the deep venous system is edema. Unilateral edema of the leg or asymmetrical bilateral edema should be considered as diagnostic of deep venous thrombosis unless another cause can be definitely proved. Unfortunately, because of the frequent association of congestive heart failure and thromboembolism, apparently equal edema of both legs will often be present to confuse the clinical picture. In this situation, however, edema is often more marked in the leg involved.

The Septic Form of Deep Venous Thrombosis ("Septic Thrombophlebitis"): Since the advent of antibiotic therapy, this form of thromboembolic disease is rare. Fever is frequently higher than that seen with aseptic venous thrombosis, but there are no specific diagnostic signs. Such a process usually occurs in association with pelvic inflammatory disease which may result from operations on pelvic structures, childbirth, abortions, appendiceal abscess, etc. Pelvic examination may reveal some tenderness, local heat, fluctuation or induration in the broad ligaments or along the pelvic floor. Fever is usually of longer duration than in the aseptic form of this disease. Not infrequently, the diagnosis becomes apparent only after septic emboli have produced septic infarcts and secondary abscesses of the lung. Diagnosis is dependent on the demonstration of some septic process in close relationship with a portion of the deep venous system.

"Trousseau Syndrome" ("Migratory Thrombophlebitis"): Thrombosis involving either superficial or deep venous segments in more than one area, either concurrently or separated by considerable periods of time, deserves special attention. A history of spontaneously developing thrombosis in superficial veins of the arm, abdomen or leg, frequently linked with venous thrombosis of the deep veins of the leg, warrants careful diagnostic work-up. The following disease entities most frequently associated with this picture are those which Trousseau originally linked with migratory thrombophlebitis: (1) thromboangiitis obliterans; (2) polycythemia rubra vera; (3) hidden carcinoma, especially of the stomach, pancreas or lung; and (4) collagen disease.

Deep Venous Thrombosis with Significant Arteriospasm (Phlegmasia Cerulea Dolens): Almost all cases of massive venous occlusion of the leg are associated with some degree of arteriospasm. One of the synonyms for iliofemoral venous thrombosis is "phlegmasia alba dolens," indicating the pallor of the leg thought to be due to spasm of the arteries accompanying the sterile inflammation of the vein. When venous thrombosis of the leg and arteriospasm are of such a degree that cyanosis (cerulea = blue) is present, a serious situation exists, and the viability of the leg may be in question. It is essential that this entity be recognized promptly and differentiated from primary arterial thrombosis or arterial embolism, since the approach to treatment is somewhat different. A pale cold leg with obvious signs of arterial insufficiency may present a difficult diagnostic problem; fortunately, in the usual case of phlegmasia cerulea dolens, marked edema of the leg is present. Such a finding associated with signs of acute arterial insufficiency should suggest the presence of a thrombus involving the venous system. One should not expect to see edema of the leg in the early phase of primary arterial obstruction; secondary venous occlusion may occur after a period of complete arterial occlusion, but it is not an early finding. Rarely, massive venous occlusion and the associated arteriospasm may occur so rapidly that there is no time for edema to develop. In these instances, we believe that rapid institution of specific treatment for phlegmasia cerulea dolens (continuous epidural sympathetic block and intravenous administration of heparin) is imperative. These measures will not interfere with subsequent therapy if it is later decided that the primary abnormality is arterial thrombosis or embolism. Arteriospasm will usually be promptly relieved by this regimen. If arteriospasm remains unrecognized for a considerable period of time, secondary arterial thrombosis may supervene, and the venous thrombosis becomes more extensive. In these cases, the prognosis for survival of the leg is poor; arterial thrombectomy is of little value since massive venous occlusion usually prevents the re-establishment of adequate arterial outflow.

Pulmonary Embolism: All too frequently the first clinical sign of a thrombus in the leg or pelvic veins is one of the cardiorespiratory manifestations of pulmonary embolism. Here, as with deep venous thrombosis, clinical recognition is the exception rather than the rule. Even when an embolus has occluded a major branch of the pulmonary arterial tree, there may be no definite sign to aid in the diagnosis. In our studies of 606 patients with pulmonary emboli proved at autopsy, a definitive diagnosis was made prior to death in only 7 per cent of the cases. Diagnostic failure was usually due either to the minimal period of time between onset of symptoms and death or to the obscure nature of the clinical manifestations of the pulmonary embolus. Of those patients in whom pulmonary embolism was thought to be a major factor in producing death, one-fifth died almost immediately, and almost half of the patients were dead within fifteen minutes. This leaves little time for careful evaluation and the initiation of treatment.

Assessing 501 embolic episodes in 383 patients with significant pulmonary embolism (i.e., embolism which was a major contributory factor or the sole cause of death), it was found that pulmonary embolism without infarction was responsible for few if any characteristic signs or symptoms. Pulmonary embolism without associated infarction may result in sudden death or there may be shortness of breath, hypotension or cyanosis. Chest pain is extremely rare, and, if present, is usually a transitory dull precordial discomfort.

If pulmonary infarction is present, typical or atypical pleuritic chest pain is more frequent, although it is still found in less than half of the patients. Hemoptysis occurs only when infarction is present and then only in one patient in five.

A peripheral infarct will occasionally produce a friction rub, but this finding is rare. However, friction rubs are frequently missed because they are transitory. To detect this abnormality the

chest of a patient with suspected pulmonary embolism must be examined at repeated intervals.

The so-called classic triad of chest pain, shortness of breath and hemoptysis was found in only 3 per cent of major embolic episodes occuring in our patients.

A sense of awareness of the variable and frequently obscure manifestations of pulmonary embolism should alert the clinician to the possibility that this condition may exist in a patient with unexplained dyspnea, hypotension or chest pain. The presence of hemoptysis or friction rub should be considered evidence of pulmonary embolism until proved otherwise. Since the manifestations of this disorder are so vague, any suspicious sign is sufficient justification for the immediate institution of adequate treatment.

Aids in the Prediction and Diagnosis of Thromboembolic Disease

EPIDEMIOLOGIC CONSIDERATIONS

Certain factors in the history and general medical evaluation may help in making the decision as to treatment of an equivocal case and in the selection of patients for prophylactic therapy. Previous studies[3] have indicated that the incidence of thromboembolic disease is much higher when certain epidemiologic factors are present.

Prior History of Thromboembolic Disease: A prior history of deep venous thrombosis or pulmonary embolism, no matter how remote, is of such ominous prognostic import that we recommend prophylactic anticoagulant therapy in any patient with such a history who requires any significant restriction of activity. Patients in this group with suspicious signs referable to the legs or chest should receive immediate treatment.

Heart Disease: When all patients with heart disease (including those not in heart failure) are considered, pulmonary embolism is three and a half times more frequent in this group of patients than in those without heart disease or cancer. The presence of auricular fibrillation or congestive heart failure increases the incidence about tenfold.

Cancer: Malignant neoplasms of the gastrointestinal tract, lung, or genitourinary tract increase the risk of thromboembolism about fourfold. Other neoplasms have a much lesser effect.

Trauma to the Leg: Bauer[4] has reported an eightfold increase in thromboembolic complications following trauma to the leg.

Obesity: Extreme obesity is associated with a twofold increase in the risk of thromboembolism.

Immobility: Gibbs[5] has shown a direct relationship between the degree and length of immobility and the incidence of thromboembolic disease. Regardless of the reason for the immobility (operation, fracture, paralysis, serious medical illness), this appears to be a critical factor.

The presence of one or more of these epidemiologic factors should make one more willing to treat an equivocal case in which clinical evidence alone is inadequate to make a definitive diagnosis.

CLINICAL TESTS

Venous Thrombosis: It is our impression that Homans' sign (pain in the calf on dorsiflexion of the foot) is of little or no value in diagnosis because of the high percentage of false positive and false negative results. Tenderness on direct palpation over the course of the deep venous system is much more specific; in the absence of demonstrable tenderness by this approach, we discount the significance of Homans' sign. Measurements of the leg taken at different levels, carefully determined from a fixed point (the superior margin of the medial malleolus), are of real value.

A more objective evaluation of pain of the calf or thigh may be obtained by slowly inflating a sphygmomanometer cuff placed about the part. Lowenberg[6] reports that the pressure at which the patient notes pain is considerably lower when venous thrombosis is present. Our experience with this test is limited, but it deserves more extensive use to determine its value in detecting subclinical cases of deep venous thrombosis.

Occasionally, in a patient with pain of an equivocal nature in one leg, we have injected intravenously a therapeutic dose of heparin (75 to 100 mg.); relief of pain following this procedure is taken as additional suggestive evidence of deep venous thrombosis.

In the past, our laboratory has evaluated a number of tests of various components of the clotting mechanism. None has proved of value, at our present state of knowledge, in detecting the tendency to, or the presence of, thromboembolic disease.

Pulmonary Embolism: Roentgenograms are of little use in the diagnosis of pulmonary embo-

lism. The roentgenographic picture of pulmonary infarction is variable and non-specific. The so-called classic example of a wedge-shaped infarction is extremely rare. The usual pulmonary infarct is a non-specific pulmonary density which is frequently mistaken for atelectasis or pneumonia. Quite frequently a small pleural effusion is present. It is our belief that *a small pleural effusion at the base of the lung with or without a demonstrable pulmonary density should be considered as suggestive roentgenographic evidence of pulmonary infarction unless another definite cause can be proved.*

The *electrocardiogram* is a frequently neglected aid in the diagnosis of pulmonary embolism. Electrocardiographic abnormalities can be found in a high percentage of patients with pulmonary emboli. Tracings should be obtained early in the course of the disease in order to obtain information of value. Serial records at frequent intervals may be helpful when characteristic electrocardiographic changes are not seen initially and when the diagnosis remains in doubt. The so-called acute cor pulmonale type of electrocardiogram is infrequently seen. The more common changes are a shift of the electrical axis to the right, incomplete or complete right bundle branch block, T wave inversion in right percordial leads, RST segment depression in left precordial leads, tall pointed P waves in the limb leads ("P pulmonale") or the onset of an atrial arrhythmia.

While these specific findings often support the clinical diagnosis of pulmonary embolism and, in certain combinations, may even be strongly suggestive of this condition, the evolution and regression of the electrocardiographic abnormalities are equally important. When these changes result from pulmonary embolism, they usually revert toward normal in a matter of several days or weeks. Tracings taken before the suspected embolism, if available, are valuable for purposes of comparison.

Complications and Sequelae of Deep Venous Thrombosis

Severe Arteriospasm (Phlegmasia Cerulea Dolens): The problems in diagnosis and the hazards of this complication have already been mentioned.

Pulmonary Embolism: It has been estimated that, without adequate treatment, one patient in three with deep venous thrombosis will have a pulmonary embolus. Of those patients with pulmonary embolism who remain untreated, by the most conservative estimates, at least one patient in five will die from a second fatal pulmonary embolus. This means that failure to apply specific therapeutic measures to a patient with deep venous thrombosis will result in an ultimate mortality from pulmonary embolism of at least 6 per cent.

Postphlebitic Syndrome: It is our belief that the physiopathologic process responsible for the development of this syndrome is edema secondary to venous insufficiency. Once persistent edema is present, distention of tissue spaces and thinning of the skin occur resulting from the increased skin tension. The thin edematous skin is more susceptible to trauma and secondary infection. Persistent inflammation is followed by induration, decrease in local arteriolar blood supply secondary to focal scarring and ultimately, ulceration. Bauer[7] has shown that as the time of observation after the acute thrombotic episode increases, there is a progressive increase in the incidence of indurative and ulcerative changes. Follow-up studies on patients, five to fifteen years after the acute episode, have demonstrated an incidence of ulceration of the leg in the range of from 20 to 40 per cent; Bauer[7] has observed an even higher incidence (all in untreated patients). Zilliacus[8] has reported that of 680 patients surveyed from six to fourteen years after their thrombotic episode, only 6 per cent had completely normal legs; 10 per cent were totally incapacitated and unable to work and another 16 per cent had had to change their occupations. These observations indicate that acute venous thrombosis and the sequelae of edema, inflammation, induration and ulceration represent a disabling disease of major magnitude.

Treatment of Thromboembolism

The tentative diagnosis of thromboembolic disease is an indication for immediate treatment. The objectives of treatment are to shorten the period of disability and lessen the incidence of complications of deep venous thrombosis. We believe that the optimal treatment is prompt and effective anticoagulant therapy. With this form of treatment both mortality rate and postphlebitic sequelae have been less than during the period when ligation of the femoral vein was practiced.

Heparin Therapy

Intermittent Intravenous Injection: One may obtain an almost instantaneous anticoagulant effect with the intravenous administration of heparin (10 mg. per ml.) in doses of 75 to 100

mg. More concentrated forms of heparin may result in local burning pain at the site of intravenous injection. Therapy can then be continued with any of several technics. Intermittent intravenous injection of heparin in doses of 75 to 100 mg. at eight-hour intervals has been proved by a number of Scandinavian workers to constitute satisfactory therapy, as indicated by a reduction of thromboembolic complications. This regimen provides a "picket-fence" response, clotting times usually returning to normal within five hours after administration of 100 mg. of heparin. The alternating return of clotting times to normal values does not appear to diminish the effectiveness of this therapy. Although not absolutely essential, it is wise to check at least one clotting time, just prior to a dose of heparin, to be certain that there is no cumulative effect from prior doses.

Subcutaneous Injection: An alternative method is the administration of concentrated aqueous heparin (100 to 200 mg./ml.) subcutaneously at twelve-hour intervals. Individual doses vary from 100 to 300 mg. The advantage of this method is that heparin may be administered by the nursing staff in hospitals which require that a physician personally administer intravenous medications. The disadvantage is that repeated determinations of clotting time are necessary to adjust dosage to assure adequate effect without risk of hemorrhage. An adequate anticoagulant effect will not be obtained by this approach in a small percentage of patients, presumably because of heparin-inactivating enzymes present in the subcutaneous tissues.

In the past, several heparin preparations incorporated in slowly absorbable menstrua have been used in deep subcutaneous injection. We have abandoned these because of the frequency of pain and hematomas at the site of injection and because of a somewhat unpredictable response.

Continuous Intravenous Infusion: In rare instances involving patients with a potential source of major hemorrhage, there may be some advantage to the administration of heparin by constant intravenous infusion. Aqueous heparin, 250 to 300 mg., is placed in 1,000 cc. of 5 per cent dextrose in water and infused, usually at a rate of 20 to 30 drops per minute, so that there is at least a twofold prolongation of the clotting time. This procedure obviates the extreme prolongation of clotting time which occurs immediately after the rapid administration of a single dose of heparin. Use of this technic requires rigid control of the rate of intravenous infusion to prevent excessive prolongation of the clotting time and the risk of serious hemorrhage.

Bleeding Due to Heparin: One of the major advantages of heparin as an anticoagulant is that its effects on the clotting mechanism may be immediately reversed, in the event of bleeding or if the need for an emergency operation arises, by an intravenous injection of protamine sulfate, usually in an amount equal, milligram for milligram, to the last dose of heparin. It should be remembered that in cases of bleeding following subcutaneous administration of heparin, half the protamine should be given by prompt intravenous injection and the remainder by constant intravenous infusion over the period required for absorption into the blood stream of the heparin remaining in the subcutaneous depot.

ORAL ANTICOAGULANTS

Oral anticoagulants provide greater convenience in the management of the usual case of thromboembolic disease. The initial dose of one of the drugs of the coumarin or indandione groups is given at the time of the first dose of heparin. Heparin is continued until the Quick prothrombin activity has reached a satisfactory level. It is essential that the initial and subsequent blood specimens drawn for prothrombin determinations be obtained at a time when the heparin effect has completely subsided, since some of the extraneous, predominantly physical, effects of heparin may produce falsely low prothrombin activity values. Subsequent doses of the oral anticoagulant are determined on the basis of daily Quick prothrombin activity levels. Except in unusual circumstances, daily prothrombin times should be obtained for all hospitalized patients receiving anticoagulants, regardless of the particular agent being used.

There is considerable variation in opinion as to what constitutes effective therapy with oral anticoagulants. Until recently we have attempted to maintain values between 15 and 30 per cent activity. A statistical study,[9] however, did not yield proof that a lesser effect was associated with any higher incidence of thromboembolic complications. For this reason, for the past several years, we have maintained half of our patients treated with anticoagulants in the 30 to 50 per cent Quick prothrombin activity range; it is still too early to obtain valid statistical data with regard to the comparative inci-

dence of bleeding and thromboembolic complications in the two groups.

Advantages of Various Oral Anticoagulants: It is our current opinion that there is no major therapeutic advantage of one oral anticoagulant over another. Our experience with all the clinically available coumarin and indandione derivatives indicates that the thromboembolic complication rate is not significantly lower with one agent than with another. Adjustment of drug dosage to maintain relatively constant prothrombin activity values is easier with some agents than with others. It is preferable to gain extensive experience with one anticoagulant, and this in itself facilitates proper management of dosage. Our own personal preference in treating hospitalized patients is to use a short-acting anticoagulant, such as phenylindandione, which can be given on a twice-daily dosage schedule, or, rarely, once a day in circumstances of extreme drug sensitivity. This system has the advantage that only half of each day's dose of anticoagulant has been given at the time that the daily prothrombin activity report is reviewed. When therapy is to be interrupted for any reason, the return to normal prothrombin activity levels is relatively rapid. The long-acting drugs can be administered in a single daily dose or as infrequently as once every two to five days. It seems simpler to us to give doses of a drug at 24-hour intervals rather than to gauge dosage by waiting for prothrombin activity values to jump to higher levels. Other investigators believe that the long-acting anticoagulants are best given by a schedule of administration in which a subsequent dose of the drug is given only when prothrombin activity values indicate that the patient is escaping from the desired therapeutic range.

Hemorrhage Due to Oral Anticoagulants: Bleeding due to any of the oral anticoagulants can be controlled by the intravenous or oral administration of vitamin K_1 in doses of 5 to 50 mg. Except in rare instances of hemorrhage secondary to gross overdosage, bleeding will stop within four to eight hours, sometimes less, after the administration of vitamin K_1. Minor bleeding, when continued anticoagulant treatment is contemplated, is best controlled by decreasing the anticoagulant dosage or by giving small amounts of vitamin K_1 (5 to 10 mg). Larger doses of vitamin K_1 may be followed by a prolonged period of refractoriness to the effects of oral anticoagulants.

The incidence of hemorrhagic complications in our series of patients treated with anticoagulants for deep venous thrombosis and/or pulmonary embolism was 14.8 per cent. Most of the episodes were of a minor nature and did not interfere with continuation of treatment. Major bleeding (requiring blood replacement and/or cessation of anticoagulants) occurred in 2.4 per cent of the treatment courses; in almost every instance this major bleeding took place in an operative wound or at the site of a preexisting gastrointestinal lesion. Bleeding was successfully controlled by the regimen described in every instance.

Duration of Anticoagulant Therapy: As yet there is no conclusive information with regard to the duration of anticoagulant therapy required to minimize thromboembolic complications. Analysis of our patients in whom such complications developed during or within twelve weeks after the termination of therapy permits several tentative conclusions. Anticoagulant treatment should be continued until the patient is free of all signs and symptoms *and* fully ambulatory. Failure to comply with either of these criteria will lead to a higher complication rate. We have also found that added care is necessary in the treatment of patients with heart disease in whom embolic complications are more frequent. Our complete analysis of the effectiveness of anticoagulant therapy has been previously published[9]; it should be stressed here, however, that fatal pulmonary emboli subsequent to the initiation of anticoagulant treatment were four times more frequent in those patients who had one or more pulmonary emboli before the diagnosis was made and therapy instituted. No anticoagulant will dissolve existent thrombi; the functions of anticoagulant agents are to prevent further propagation of a fresh friable thrombus and to permit organization of the thrombus already present.

PLASMIN AND PLASMIN ACTIVATORS

There has been considerable enthusiasm in the past several years concerning the role of plasmin and certain plasmin activators (streptokinase, urokinase) in the treatment of thromboembolic disease. Good objective evidence that these agents reduce either morbidity or mortality from thromboembolic disease is lacking at the present time. Years of competent investigative work and accumulation of statistical data will be necessary before the value of these agents can be determined. There are no

well controlled studies to suggest that intramuscular or sublingual enzyme preparations have any value whatsoever. A number of laboratories, including our own, have shown that circulating fibrinolytic enzyme has a profound effect on the proteolytic degradation of fibrin and fibrinogen. However, a blood clot and an intravascular thrombus should be considered as separate and distinct entities. The intravenous administration of high concentrations of non-pyrogenic plasmin or plasmin activator to a patient with a thrombus less than seventy-two hours old may subsequently be shown to be an effective and safe method for complete and permanent dissolution of intravascular thrombi; however, until this is conclusively demonstrated by objective technics, these agents should be restricted to clinical investigative use.

VEIN LIGATION

The indication for vein ligation, in our opinion, is the presence of a contraindication to, or the failure of, anticoagulant therapy. Contraindication to the use of either heparin or oral anticoagulants is limited to those patients in whom the risk of bleeding is so great, or in whom the result of bleeding would be so serious, that the use of any drug which will alter the clotting mechanism is not warranted. Patients who have had recent operations on the eye, brain or spinal cord or with a history of recent cerebral hemorrhage and those who have had a recent prostatectomy, particularly by transurethral resection, fit into this category.

Progression of venous thrombosis or recurrent pulmonary embolism seems to occur more frequently during treatment with oral anticoagulants than with heparin. When this occurs, heparin therapy should be instituted and, in most instances, no further complications will result. However, if a second complicating pulmonary embolus should occur, operative treatment is recommended.

Vena Cava Filter: Since the development by DeWeese and Hunter[10] of a "vena cava filter" we have recommended this procedure as the operation of choice. This technic involves the placement in the inferior vena cava just below the renal veins of one or two rows of interlacing angulated silk sutures which tend to trap any dislodged emboli. It has the advantage of removing any emboli of significant size from the venous circulation without resulting in complete interruption of caval blood flow, which would occur with ligation. Extensive animal studies and the results in five human subjects with multiple prior pulmonary emboli have shown this to be a safe and effective procedure, not followed to date by the extremely disabling sequelae associated with caval ligation. In all five patients on whom this operation was performed the indication was repeated pulmonary emboli, rather than contraindication to anticoagulant therapy, therefore, it was possible to administer anticoagulants during the postoperative period; this may have helped to minimize thrombosis around the silk suture material until pseudoendothelialization had taken place.

Femoral or Vena Caval Ligation: We have commented in the past on the fallacy of reliance on superficial ligation of the femoral vein as a measure to prevent pulmonary embolism. As McLachlin and Paterson[11] have shown, over half of deep venous thrombi are found in locations where bilateral superficial ligation of the femoral vein will not prevent subsequent embolism. Bilateral common femoral or vena caval ligation are more effective but are associated with a much higher incidence of postphlebitic sequelae; in addition, all these procedures have been followed by a significant postligation mortality from fatal pulmonary emboli arising from thrombi propagating just proximal to the site of ligation. It is for these reasons that we restrict our operative procedures to the indications listed herein, and prefer to continue our evaluation of the vena cava filter rather than to carry out ligation *per se*.

EPIDURAL SYMPATHETIC BLOCK

Brief comment has been made previously on additional measures of value in the treatment of phlegmasia cerulea dolens. If there exists arteriospasm of a degree sufficient to compromise the arterial circulation, immediate treatment is essential. Continuous epidural sympathetic block should be instituted by insertion of a polyethylene catheter into the epidural space with intermittent injection of a local anesthetic for periods of several days to a week or longer. To minimize the possiblity of local bleeding it is essential that the catheter be inserted prior to the beginning of heparin therapy. It is our impression that the latter agent is the preferable anticoagulant because of its apparent beneficial effect in relieving vasospasm. Rapid improvement is usually observed; epidural catheters have been kept in place for as long as ten days but can frequently be removed

within forty-eight to seventy-two hours while heparin therapy is continued for a considerably longer period.

ANCILLARY MEASURES

The ancillary non-specific measures used in the treatment of thromboembolism are well known and include bed rest until signs and symptoms subside, repeated careful elastic bandage wrapping of the legs, elevation (6 to 8 inches) of the foot of the bed and finally, progressive ambulation with adequately wrapped legs while anticoagulants are still being administered. Antibiotics have no place in the therapy of the uncomplicated aseptic form of deep venous thrombosis. Prophylactic antibiotics may be of value in patients with pulmonary embolism to reduce subsequent secondary infection of pulmonary infarcts.

True septic thrombophlebitis is a separate and distinct disease entity. Pathologically, bacterial colonies are demonstrable in the thrombus. The high frequency of septic emboli in this condition makes the treatment of choice specific antibiotic therapy and vein interruption well above the site of thrombosis with subsequent anticoagulant therapy to prevent secondary propagation of thrombus proximal to the site of ligation.

TREATMENT OF PULMONARY EMBOLISM

The therapeutic measures used to treat acute pulmonary embolism seem to have little effect in altering prognosis. The administration of narcotics, oxygen, aminophylline, atropine or papaverine may provide symptomatic relief but they have not been shown to lessen mortality either experimentally or clinically. The use of norepinephrine to treat hypotension secondary to acute cor pulmonale has been shown to alter the mortality rate from experimental pulmonary embolism in dogs[12] and may have some specific value in man. Unfortunately, fatal embolic episodes in our series produced death in almost half of the patients in less than fifteen minutes from the onset of symptoms; this leaves little time in such a group at least for the institution of specific therapy, even if it were available.

PREVENTION AND TREATMENT OF EDEMA

The treatment of deep venous thrombosis does not end with the acute episode. It is essential that the patient be instructed in a program which will prevent the development of edema, since this is the first and essential element in the progressive pathologic changes which result in the full postphlebitic syndrome. Our patients are instructed to wrap their legs to the knees with elastic bandages before they get up in the morning and to wear these supports as long as they are on their feet for a period of from six weeks to six months. A trial at full activity without support is then begun; if any edema of his legs develops, the patient returns for measurement and fitting of elastic stockings designed and made to fit his edema-free leg. In addition, these patients are instructed to sleep with the foot of the mattress elevated 6 to 8 inches. Rest during the day with the legs elevated is advised if any discomfort is noted.

It is important that elastic stockings be individually constructed to the patient's own leg measurements. Hydrodynamic studies have shown that valvular incompetence in the recanalized deep venous system results in persistent elevation of venous pressure comparable to the pressure exerted by a column of water reaching to heart level. Pressure is greatest at the level of the ankle and foot and progressively decreases as one moves up the leg. It is important that elastic stockings are made to counteract these pressure relationships by exerting the greatest pressure at the ankle area, with progressively less compression further up the leg. The form of the stocking will vary with the contour of the individual leg. If the pressure does not progressively decrease, there may be an area of too great venous compression at one point, which may actually hamper venous return and do more harm than good.

Patients who have carefully followed this regimen from the time of the acute thrombotic episode have been free of advanced skin change and ulceration. Occasionally pain in the leg or fatigue may occur, but the disabling sequelae do not.

PREVENTION OF THROMBOEMBOLISM

Prior comments on the extreme difficulty and the inaccuracy of the clinical diagnosis of thromboembolic disease were not meant to create an atmosphere of therapeutic nihilism. However, we must be realistic about what we can accomplish, even with maximal clinical diagnostic accuracy, in our therapeutic attempts to lower the disability and mortality from this disease.

Roughly, at the present time, we diagnose

about 10 per cent of the cases of deep venous thrombosis. Another 10 per cent have some localizing sign which should result in the diagnosis of this entity. The remainder, however, have no recognizable clinical signs which may be utilized for even a presumptive diagnosis. In our series at least (substantiated by others[13, 14]), the diagnosis of pulmonary embolism is less accurate. In many instances, the first pulmonary embolus is the fatal one.

Utilizing a critical approach for the analysis of the value of anticoagulant therapy, we have estimated that anticoagulant treatment, as now practiced, will salvage at least seven of every ten patients who would have died from fatal embolism had anticoagulants not been used.[9] These figures were obtained with the assumption that any unexplained sudden death occurring in a patient within twelve weeks after the termination of anticoagulant therapy was due to pulmonary embolism. The true rate of salvage with anticoagulant therapy is probably somewhat better than this.

Even assuming that the patients in whom we do make a positive diagnosis represent a higher proportion of those patients with more advanced and more serious forms of thromboembolism, it would not seem unreasonable to estimate that we treat only one patient in eight with fatal or potentially fatal (without anticoagulant treatment) pulmonary embolism. If one is willing to accept these assumptions, then it must be recognized that we will diagnose, treat and salvage only a small proportion of those patients in whom one can expect fatal pulmonary embolism to develop. Maximal improvement in our diagnostic accuracy might result in a twofold increase in the number of patients treated, but even this will represent salvage of only a small percentage of expected fatalities.

Prophylactic Anticoagulant Therapy: However, we have not yet contracted the nihilistic contagion and still regard thromboembolism as a theoretically preventable disease. Every attempt should be made to improve diagnostic accuracy and this should result in a slight reduction in disability and mortality. At our present state of knowledge, lacking a satisfactory diagnostic test, the most rational approach to a significant decrease in mortality and morbidity seems to be the utilization of prophylactic anticoagulant therapy in a selected group of patients in whom the risk of thromboembolic complications is greatest.

Utilizing some of the epidemiologic data that have been accumulated, we recommend that the clinician seriously consider the value of using prophylactic anticoagulants in those patients with a high predisposition to thromboembolic disease who must be immobilized in bed. As mentioned earlier, the greatest risk occurs in patients with a prior history of thromboembolism, in older people with heart disease or with certain types of cancer, and in any patients with trauma to the leg or extreme obesity. We now recommend prophylactic anticoagulant therapy in all patients with prior thromboembolism, congestive heart failure or extreme obesity and are planning to extend our indications to the other categories listed herein. The risks of anticoagulant therapy are far less than the incidence of thromboembolic complications in these patients. The results should justify the time and expense required to carry out such a program. Until we find methods for the early laboratory diagnosis of venous thrombosis, this seems to be the only available approach capable of effecting a significant reduction in the incidence of this disease.

Summary

The manifestations of thromboembolism are highly variable and frequently obscure. Clinical diagnosis of these entities is difficult, and the majority of cases will not be diagnosed by the means presently available to us. Nevertheless, a heightened awareness of the vagaries of this disease can result in considerable improvement in diagnostic accuracy. Prompt diagnosis on the basis of the slightest clinical suspicion, followed by immediate and adequate anticoagulant therapy, should result in a measureable decrease in thromboembolic complications. However, if one hopes to achieve a profound reduction in incidence of thromboembolism, the only approach presently available is prophylactic rather than therapeutic. The use of measures to increase venous return in patients who are immobilized in bed, plus the institution of prophylactic anticoagulant therapy in a selected group of patients with a high predisposition to the development of thromboembolic diseases, should result in a significant reduction in disability and mortality from this theoretically preventable disease.

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Diagnosis and Surgical Approach to Aorticoiliac Arterial Disease*

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BECAUSE of the development of technics of direct approach to problems at all levels in the aorta and in the iliac systems, much has been added to clinical diagnosis of these lesions. This phase of surgical treatment began in 1951 when, for the first time, an aneurysm of the abdominal aorta was resected and replaced with a homologous artery graft by Dubost.[1] At a rapid rate the new concept of resection and replacement of this major artery when diseased was applied by others in this country[2–4] and a massive literature has developed in this field.

It is unfortunate that the progress in surgical technic has not been paralleled by similar progress in the field of prevention of the lesions for which surgery is applied or by a real understanding of the pathologic processes which are concerned.

At the present time the mass of aorticoiliac disease is generally considered to be due to a degenerative and metabolic change lumped together under the general term of arteriosclerosis or atherosclerosis. In the case of aneurysm, this could be justified only in that the destruction of the elastic structures in the vascular wall is probably the primary factor in pathogenesis. When this is not produced by a syphilitic or a pyogenic infection carried to the artery by a mycotic embolus, its fundamental cause is no more accurately known than to say that the process is degenerative. Actually, multiple etiologies of the destruction of the elastic layers of the artery must be suspected. These could include any variety of inflammatory disease or any disturbance of enzymatic activity in addition to the simple mechanical degeneration resulting from aging.

Occlusive disease of the aorta and iliac systems provides an even more attractive field for conjecture as to multiple etiology, in contradistinction to the single entity of arteriosclerosis. The surgeon finds distinctly different gross characteristics of the involved aorticoiliac system in patients suffering from chronic occlusion in this area. In some of these the lesion is localized to the intima and the subjacent media. In others, extensive medial changes, including calcification, are encountered. In still others the thick, occluded vessel is notably adherent to the surrounding tissues. These latter cases strongly suggest to the surgeon, in dissecting in this area, that an inflammatory process is responsible for the adhesions if not for the arterial lesion.

From a practical point of view, leading to proper diagnosis and surgical approach, diseases of the aorticoiliac system are those which appear as acute occlusions, chronic occlusions and dilatations of the vessels.

ACUTE OCCLUSION OF ABDOMINAL AORTA AND ILIAC ARTERIES

Acute aortic occlusion secondary to embolism is rarely encountered at any level other than the aortic bifurcation and presents a clinical picture not different from embolic occlusion of the common iliac bifurcations occurring simultaneously. This catastrophe, which carries urgent surgical implications, has in our experience to be differentiated from three other conditions: (1) acute thrombosis of the aorticoiliac system which in almost every instance has previously been the site of partial occlusion due to arteriosclerosis; (2) dissecting hematoma or dissecting aneurysm of the aorta and (3) the general effect of hypotension, secondary to myocardial changes, occurring in a patient with incomplete occlusion of the aortic bifurcation. Each of these conditions presents the picture of a major occlusion affecting the arterial supply of the lower ex-

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tremities, and in each case certain more or less differentiating features are present.

DIFFERENTIAL DIAGNOSIS

Associated Cardiac Conditions: Most arterial emboli lodging at the aortic bifurcation or at both iliac bifurcations after splitting at the aortic bifurcation are large. They arise from thrombi which develop within the heart chambers and are rarely seen in patients who do not exhibit one of two cardiac conditions, namely, auricular fibrillation and myocardial infarction. The arrhythmia of auricular fibrillation produces sufficient stasis within the left atrium for the development of a large thrombus. The auricular fibrillation may be a result of arteriosclerotic heart disease, hyperthyroidism or rheumatic heart disease. If the element of mitral stenosis is present in addition to the fibrillation, the incidence of such emboli is greater because the stasis within the chamber is increased by the stenosis. Myocardial infarction secondary to coronary artery occlusion produces the second mechanism by which intracardiac thrombi develop. In this condition, the subendocardial necrotic patch of myocardium produces changes which characteristically lead to the development of a mural thrombus. Many of the mural thrombi undoubtedly remain securely attached and organize with the healing of the infarct. When a thrombus becomes free of its attachment to the myocardial wall, the detachment is likely to occur between the fifth and the twelfth day after the original infarct. Although intracardiac thrombi almost certainly develop without demonstrable reason, the majority of patients exhibiting an acute occlusion of a major vessel, such as the aortic bifurcation, will exhibit one of these two cardiac conditions, and their presence is presumptive evidence for the diagnosis of embolus as the cause of the occlusion. One of these two cardiac conditions was present in each of the authors' present series of twenty-five cases of embolism of the aortic bifurcation.

Clinical Signs: The *symptoms of the acute arterial occlusion* at the aortic bifurcation level consist of pain and loss of function. The pain is not an entirely consistent symptom, being absent in about 20 per cent of cases. When present, it is often severe, acute and continuous, rather than intermittent. Freedom from pain in any individual case probably results from a particularly severe ischemia of the peripheral nerves, rendering them functionless rather acutely. The patient complains of a numbness of the extremities and is always found to have both paralysis and loss of sensation. The anesthesia does not usually extend higher than the mid-thigh level. Paralysis is confined to the muscles of the foot and calf. Motion of the hip is retained, and the extensors and flexors of the knee are little affected.

Aortic Embolism vs. Dissection: Anesthesia extending to a point higher than mid-thigh and loss of motor function of the muscle groups of the thigh strongly suggest that the cause of the acute occlusion is a dissecting aneurysm of the aorta rather than an embolus lodged at the aortic bifurcation. In dissecting aneurysm, the occlusion of branches of the thoracolumbar aorta, due to the separation by the pulsating hematoma of the layers of the vessel, produces ischemia of the cord to a much higher level than occurs with embolism localized to the bifurcation. The high level of the ischemia resulting from dissection is also noted in the fact that changes in skin color, which in embolism are localized to the extremities from the mid-thigh level, often extend to include the hips and, occasionally, the flanks and the skin of the abdominal wall.

Loss of femoral arterial pulsation is not always complete in acute occlusion of the aortic bifurcation. Occasional retention of palpable pulses at this level is probably due to transmission of the systolic thrust through the embolic mass. In dissecting aneurysm, pulsations at the femoral level may be quite strong in spite of the effective obstruction to useful blood supply through the branches of the entire abdominal aorta, iliac and femoral systems. The palpable pulse in this instance is transmitted through the secondary or dissected lumen. The combination of palpable pulses at the femoral level with unusually high loss of sensation and the presence of all indications of acute ischemia of both lower extremities has not been met with except in cases of dissecting aneurysm.

Thrombosis of the aortic bifurcation and the iliac arteries occurs almost without exception in patients who have a significant degree of pre-existing chronic arteriosclerotic occlusion in this area. Because of such pre-existing partial occlusion, some degree of collateral circulation will already have been stimulated and the acute episode is likely to be much less severe than that experienced by a patient having an embolic occlusion of a previously normal artery. The severity of the acute symptoms may be said to be proportional to the size of the previously con-

stricted lumen which has suddenly thrombosed. Insidious thrombosis of the aortic bifurcation, or Leriche syndrome, which will be discussed later, frequently develops without any acute episode in the patient's history.

TREATMENT OF ACUTE AORTICOILIAC OCCLUSION

Except in rare instances, the course followed by a patient with an acute aorticoiliac occlusion is that of unremitting ischemia of the lower extremities leading to extensive gangrene and usually death, unless the occlusion is removed surgically. Exceptions to this usual course are occasionally observed in patients who at first exhibit all the signs of complete occlusion of the aortic bifurcation and in whom reformation of the arterial pathway is later observed. The possible explanations of this phenomenon include dissolution of an unusually soft embolus or the compression of the embolus into a major branch, such as the internal iliac artery, allowing the principal channel to be cleared. Three undoubted instances of this course have been observed by us. In these cases, restoration of circulation occurred within three hours of the onset, and if one is to treat any case expectantly, it is believed that three hours should be the maximum limit before surgery is instituted. In patients having only a modest acute ischemia secondary to thrombosis of a remaining quite small lumen in an arteriosclerotic aorta, operation may be delayed and performed later. In other instances of severe symptoms from a thrombosis and, in our opinion, all instances of an embolic occlusion, surgery should be undertaken as an emergency measure, allowing only reasonable time for essential medical supportive therapy. The success of surgery is limited in the case of embolus only by the time which has elapsed since the occurrence of the embolism and by the severity of the etiologic cardiac factor (Table I). In acute thrombosis, good results

TABLE I

Results of Aortic Bifurcation Embolectomy in Twenty-Five Cases

Circulation restored	15
Deaths	5

are limited by the general condition of the patient and in a major degree by the severity of the underlying arteriosclerotic process found in the region of the acute occlusion.

It is usually true that cardiac patients who have an embolism of the aortic bifurcation are outstandingly poor surgical candidates. In such persons, however, the prognosis without relief of the obstruction is so bad as to make surgery mandatory. The operation must in the vast majority of cases be performed through a celiotomy incision of major proportion. It can usually be done quite rapidly, however, and with superior anesthesia may be tolerated by the patient.

Not too much time need be spent in the preoperative differential diagnosis between embolism and thrombosis when the patient's course indicates surgery. The diagnosis is made at surgery and an embolus is removed by simple arteriotomy, while a thrombosis must be subjected to treatment which is governed by the character of the vessel involved. The operation in the latter instance assumes the proportions of surgery for chronic occlusion of the aorticoiliac system. Fortunately, the acute cardiac factor is less likely to be as severe in these patients as in those who need only be subjected to the relatively simpler embolectomy.

Chronic Occlusion of Abdominal Aorta and Iliac Arteries

As indicated previously, there is reason for dissatisfaction with the presently known etiology of chronic occlusion of major blood vessels. The wide variation in the gross characteristics of vessels chronically occluded has already been mentioned as one of the reasons for this dissatisfaction. Tremendous variations in the distribution of occlusive lesions of major vessels supplying the lower extremities provide another puzzle not explained satisfactorily by the broad term, arteriosclerosis.

DIAGNOSIS

A significant proportion of patients exhibiting chronic aorticoiliac occlusion have lesions which are characteristically localized to the major bifurcation. The aorta above and the iliofemoral system below are relatively little involved in the pathologic process. Whereas patients who have diffuse involvement of the vessels of the lower extremities show recognizable ischemic structural changes in the distal parts almost as soon as symptoms begin, those having localized changes at the region of the aortic bifurcation may have significant symptoms for a long time before deterioration of tissue can be observed. The symptomatology of chronically developing bifurcation occlusion is

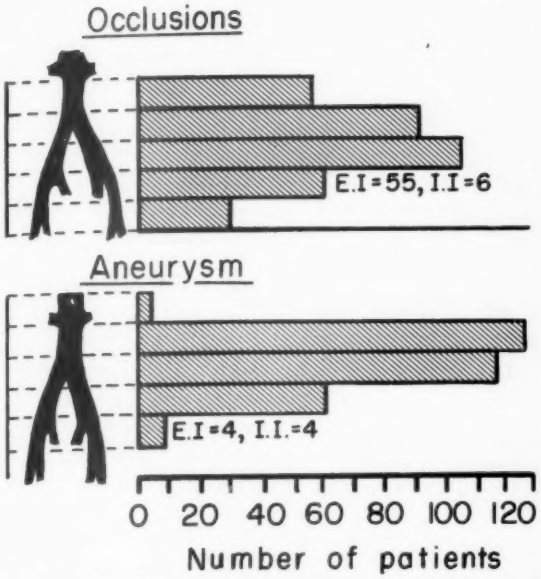

FIG. 1. Location of occlusive lesions and aneurysms of abdominal aorta and iliac arteries. E. I. = external iliac. I. I. = internal iliac.

diagnostic and is easily confirmed by the physical findings. Inasmuch as complete relief through surgical management is available to most such patients, early diagnosis is important.

Clinical Signs: The most typical symptom of occlusion of chronic development in the region of the aortic bifurcation is pain in exercising muscles (intermittent claudication). It has characteristics which immediately differentiate it from pain of any other cause. It is localized to the muscles of the foot, calf or thigh, and develops during walking, running or climbing stairs. The pain is absent during rest and, in each patient, comes on after almost exactly the same amount of exercise. The symptom is usually cramping in nature and disappears readily when the patient stands still or sits down to rest the part. Lesser amounts of walking are accomplished without complaints. Intermittent claudication shows obvious and characteristic differences from the symptoms which occur in degenerative arthritis of the spine or hips, deformities of the feet, protruded nucleus pulposus and neuritis.

In a series of 126 patients having chronic aorticoiliac occlusion, intermittent claudication was the presenting symptom in all cases. Discoloration and atrophy of the skin were present in ten, while actual necrosis of the skin was observed in eight. Impotence in patients with this type of chronic occlusion was a complaint of 42 of 101 males in the series.

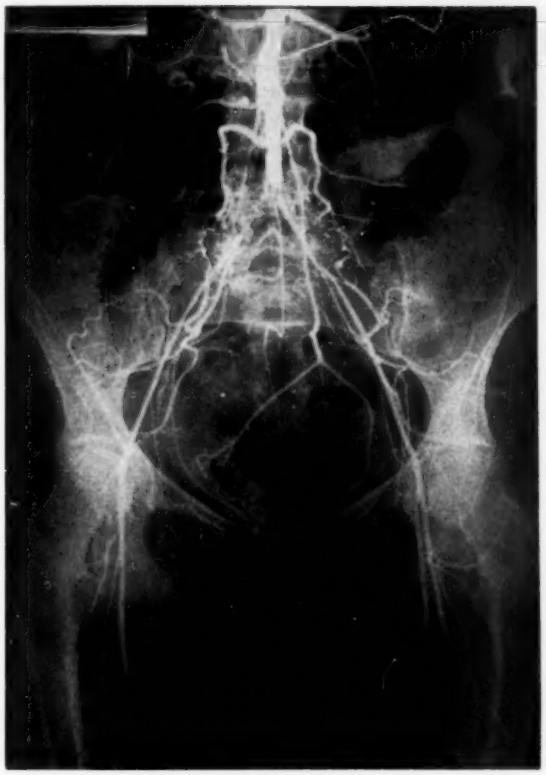

FIG. 2. Aortogram showing involvement of common iliac arteries.

The outstanding physical finding is the diminution or loss of pulsations in their normal locations in the lower extremities. In the majority of cases, the femoral pulses cannot be palpated. If a small palpable pulse remains on either or both sides in the femoral regions, it is usual to find a distinct systolic bruit over the vessel.

Distribution of Lesions: These observations pertain in a general way to the entire series of patients having chronic distal aorta or bilateral iliac disease. Consideration of the distribution of the occlusion indicates that the occlusive lesions are more frequently primary in the common iliac arteries than in any other portion of the system. In the majority the primary pathology of intimal and subintimal thickening with anatomic occlusion occurred at this level. Extension upward by the deposition of a slowly growing thrombus was the principal cause of occlusion of the lower aorta. The actual distribution of complete occlusion is shown in Figure 1, which indicates that the aorta itself was occluded either primarily by disease or secondarily by extension of the thrombus in only 57 of

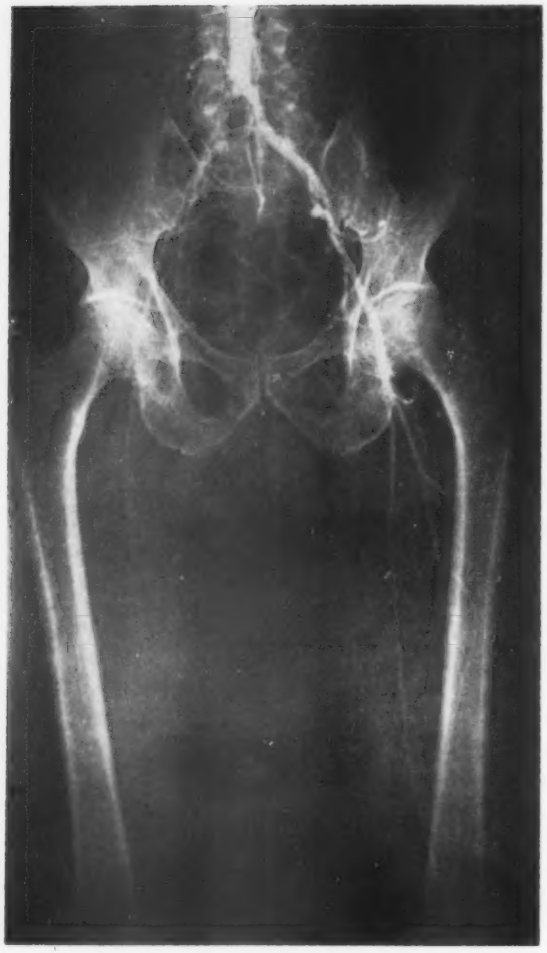

FIG. 3. Aortogram showing occlusion of right iliac and femoral systems.

126 cases. The common iliac artery, on the other hand, was primarily involved in 105 cases (Fig. 2). Occlusion of the bifurcation itself was observed ninety-one times, either as a primary or secondary occurrence. It is of interest to note in these patients, who are fairly highly selected because they are suitable condidates for surgical measures, only thirty showed occlusion in the femoral system (Fig. 3).

Clinical Course: The progressive nature of aorticoiliac occlusion has sometimes been misunderstood and complacency in its management has resulted. The clinical course of a patient with thrombosis in the region of the aortic bifurcation is distinctly one of deterioration, although periods of improvement in function frequently occur when at any stage in the progression of the occlusion the collateral artery development is permitted time to become maximum. The progression frequently is due to progressive stenosis of the arteries distal to the aortic bifurcation. It also results from a building up of the thrombus within the aorta progressively blocking the lumbar vessels which serve as collateral sources. If the distal vessels remain clear, this proximal progression is particularly dangerous if it comes to include the orifices of the renal arteries. From a surgical point of view, little difficulty is encountered in making the proximal anastomosis to the lumbar aorta, even though the occluding clot extends quite high. It is only necessary to obtain proximal control of blood flow at some point above the clot and to clear out the occluding material down to a convenient level for anastomosis. Results of such a procedure are shown in Figure 4, in which aortograms almost exactly one year apart show the progression of the occlusive disease from the level of the aortic bifurcation upward to exactly the level of the origin of the renal arteries. In this patient, a fifty-two year old woman, successful restoration of circulation resulted from the implantation of an aortic bifurcation graft of crimped Dacron®.

When progression of the disease is the result of extension of the occluding process in the distal direction, the constriction and thickening of the vessels, including segments of the popliteal artery, may in time make restoration of circulation impossible. Actually, the diminution in the size of the lumen and the efficiency of flow distal to the occlusion is, in part, due to the fact that a normal head of pressure is not being transmitted into the peripheral arterial bed. From this point of view, one may theorize that the reintroduction of good arterial flow, by restoring circulation through a bypass graft or by thromboendarterectomy, will slow down the process of occlusion in the extremities.

On the basis of the clinical course, symptoms and signs, the diagnosis of chronic arterial insufficiency due to aorticoiliac occlusion presents little problem. The importance of determining its presence stems from the fact that regional occlusions in this area are a part of a progressive phenomenon which can be predicted to become more serious and endanger the patient's extremities. Operative intervention is quite likely to be successful in well selected cases.

TREATMENT

The selection of patients for surgery depends primarily on evaluation of the character of the vessels in the lower extremities distal to the occluding

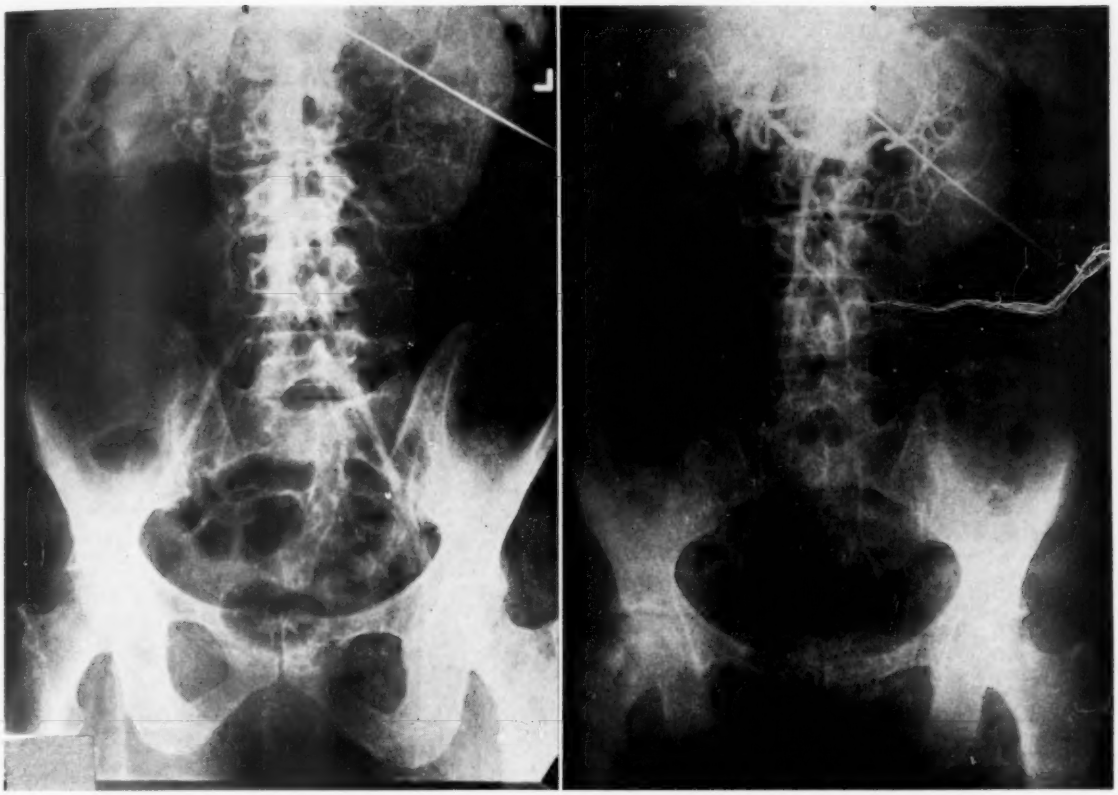

FIG. 4. Aortograms taken one year before (*left*) and just prior to aortic bifurcation graft (*right*). Note progression of occlusive disease from level of bifurcation (*left*) to level of origin of renal arteries (*right*).

lesions. Aortography was for a long time thought necessary, and in this series of 126 cases it was applied in 96 without incident. The disadvantages of aortography include such factors as the general discomfort to the patient of an additional procedure, the possibility of morbidity and mortality due to damage to the kidneys or the spinal cord, and the fact that aortograms occasionally fail to provide needed information as to the character of the femoral and popliteal arteries. For this reason, in our clinics, the routine use of aortography in evaluating patients for surgery has been abandoned. It is still used occasionally when information as to the character of the proximal aorta is important, and in patients with hypertension in whom an evaluation of the renal arteries is desired. Grading of the degree of disease in the femoral and popliteal levels is accomplished instead by direct surgical exploration when correction of the occlusion of the aortic bifurcation is attempted. The simplicity of such exploration is considered to be sufficient reason for substituting it for an aortogram.

Results of Surgery: Direct surgical restoration of the arterial flow to the lower extremities can be accomplished in two ways. The aorticoiliac occlusion may be replaced or bypassed through the use of a graft, or the aorta and iliac arteries may be thromboendarterectomized. In the presently analyzed series of 126 operations, only twelve thromboendarterectomies have been performed on the aorticoiliac system, while in 114 cases graft implantations have been performed. These have consisted of sixty-three homografts and fifty-one grafts of woven Dacron. Six patients have died, a mortality rate of approximately 5 per cent; this includes all patients dying within the period of observation.

The success of the restoration has depended to some extent on the type of operation carried out, but in general it has been quite high. In six patients who underwent resection and replacement of the aortic bifurcation, there were no failures. In sixty-eight patients who were subjected to bypass operations through the use of a graft implanted by end-to-side anastomosis, both above and below the area of occlusion, there

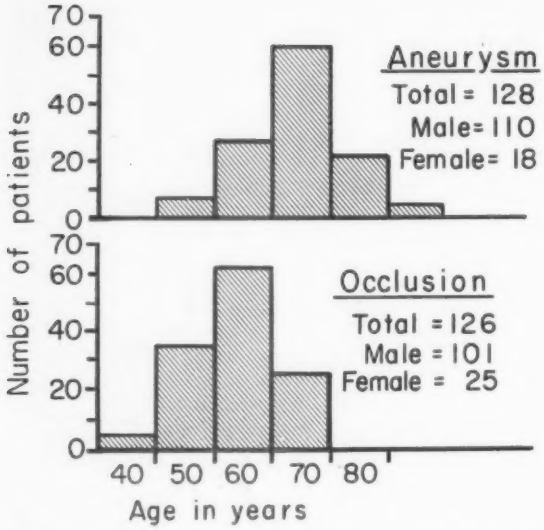

FIG. 5. Age incidence of degenerative disease of the abdominal aorta.

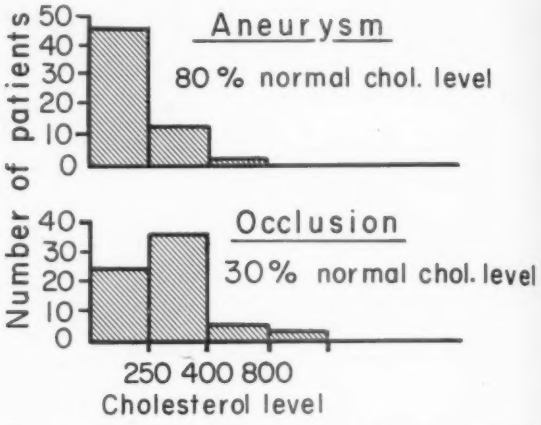

FIG. 6. Cholesterol determination in degenerative disease of the abdominal aorta.

have been sixty-three favorable results, or a success rate of 93 per cent. Thirty-six patients have required implantation of the distal end of the bypass bifurcation to the femoral artery on one or both sides. In these thirty-six patients, the procedure was successful in thirty-one (87 per cent). Thirteen patients exhibited additional severe disease of the femoral artery on one or both sides, and in these the bypass graft extended from the abdominal aorta to the popliteal artery. Of thirteen such operations twelve have been successful throughout the period of present observation. This is a rate of 93 per cent. The follow-up period in this particular series of patients is from six months to seven and a half years.

The results of the aforementioned surgical approach to the problem are good, not only from the standpoint of the restoration of pulses in the lower extremities, but also in the relief of intermittent claudication and the more advanced symptoms of arterial insufficiency.

ANEURYSMS OF ABDOMINAL AORTA

Age and Sex: A comparison of 128 cases of resection of abdominal aortic aneurysms with the foregoing series of 126 cases in which surgery was performed for occlusion of the abdominal aorta and the iliac arteries presents some interesting differences, despite the fact that both types of lesions belong to the general classification of arteriosclerosis. Figure 5 presents in graphic form the age incidence of the two conditions in these series. It will be noted that there is a definite incidence of operable aortic occlusions in the lower age group as compared with that in the group with operable aneurysms. The somewhat lesser predominance of males with occlusion as compared to those with aneurysms is probably not significant. The age incidence is, of course, highly colored by the fact that all the occlusive lesions included in the series were those which were resectable. It would, however, reflect to some degree the age at which the lesions were discovered.

Blood Pressure: When blood pressure levels in patients with occlusion are compared with those in patients with aneurysms who were examined preoperatively in their normal state, that is, not in shock because of rupture of the aneurysm, it is found that the patients with aneurysm of the abdominal aorta are more likely to have hypertension than the patients with operable occlusions of the aortic bifurcation area. It is true that this information is derived from a highly selected group of patients having occlusive disease, inasmuch as these were all operable lesions, but the data may reflect to an extent the part played by hypertension in the development of some aneurysms.

Blood Cholesterol and Hematocrit: Figures 6 and 7 portray the relationship between aneurysms and occlusion in regard to the blood cholesterol level and the hematocrit of patients in good hydration and who, in those with aneurysms, had not bled. In both instances there is considerably greater evidence of metabolic changes in patients with occlusive disease than exists in those with aneurysm. In the patients with aneurysms the blood cholesterol level was normal in 80 per cent, while in those with occlusive disease only 30 per cent had a normal level.

The hematocrit was generally higher in patients with occlusion than in those with aneurysm. In considering the significance of the comparison between the cholesterol levels, it must be pointed out that patients with abdominal aneurysms may have disturbances of nutrition due to discomfort during eating, and they frequently show weight loss.

Location of Lesion: The actual level of apparent primary lesion is somewhat different in the two conditions. Figure 1 shows graphically the area of the abdominal aorta and iliac system which may be considered to have been first involved by occlusive disease or aneurysm. The abdominal aorta itself was comparatively rarely the primary site of occlusion, while, on the other hand, it was the common site of aneurysm formation.

Arising in the region above the bifurcation of the aorta, the aneurysms rarely extend quite to the level of the origin of the renal arteries from the aorta. During the period in which we treated 128 patients with aneurysm of the abdominal aorta below the renal arteries, three aneurysms of the upper abdominal aorta including the renal arteries and the visceral branches of the aorta appeared. On the other hand, the process of loss of elasticity and dilatation commonly includes the iliac arteries, and it is not unusual to find three aneurysms, one of the distal abdominal aorta and one of each of the common iliac arteries.

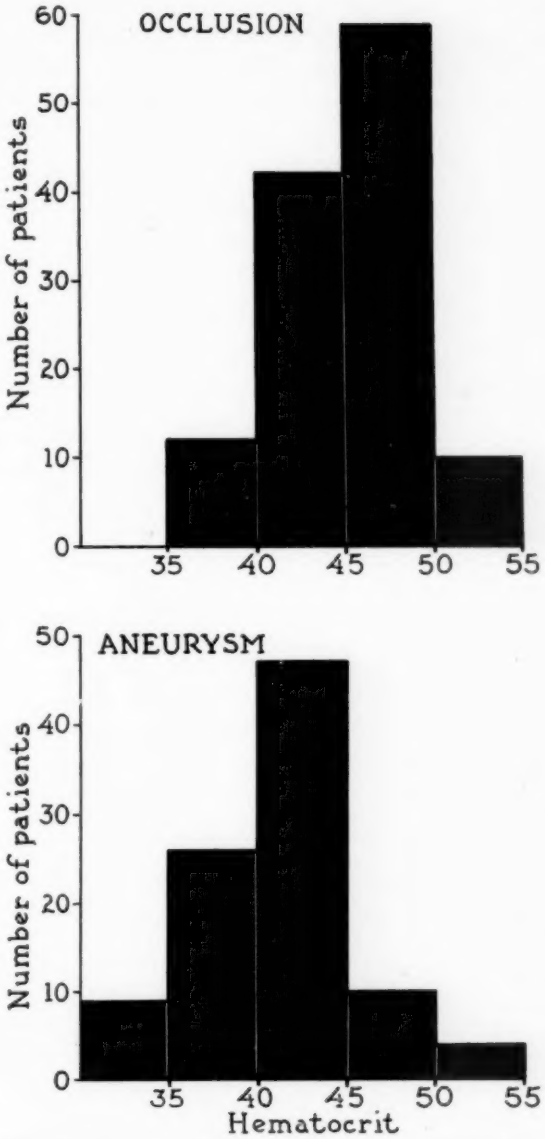

FIG. 7. Hematocrit determinations in arteriosclerotic lesions of the abdominal aorta.

CLINICAL SIGNS

Symptoms of aneurysm are often late in appearing, and there may be no complaints in a patient whose lesion has grown to the size of even 10 to 12 cm. in diameter. More often, however, complaints are produced as a result of pressure exerted by the aneurysm on surrounding structures. These include back pain sometimes extending into the thighs, resulting from pressure on the psoas muscle groups, and gastrointestinal dysfunction, due to pressure on the first portion of the jejunum or expansion of the aneurysm into the mesentery of the small bowel.

Aortic Rupture: The course of an abdominal aortic aneurysm is only occasionally long and benign. In addition to symptoms which are produced by compression of adjacent structures, the most common complication of this condition is rupture. This occurs principally into the retroperitoneal space, arising from the aneurysmal wall at its point of contact and compression against the vertebral bodies. Rupture may also take place into the mesentery of the small bowel anteriorly, into a portion of the gastrointestinal tract which has become adherent to the aneurysmal wall, and into the inferior vena cava. Rupture carries a serious prognosis, and the likelihood of its unexpected occurrence is the principal reason for quite rigid adherence to the principle that abdominal aortic aneurysms should be removed when they have been discovered whether productive of symptoms or not.

There were thirty-two instances of ruptured abdominal aortic aneurysms in the 128 resections

TABLE II
Location of Rupture of Abdominal Aortic Aneurysm in Thirty-Two Patients

Patients (no.)	Location of Rupture	Died (no.)	Mortality Rate (%)
28	Retroperitoneal space	14	50
3	Duodenum	3*	100
1	Inferior vena cava	0	0

* These 3 patients died of rerupture of graft or anastomosis.

which comprise the basis of this report. It is of maximum importance to note that among these, evidence that the patient or any physician was aware of the aneurysm before it ruptured exists in only twelve. This fact, more than the statistics which are available on the natural history of untreated abdominal aortic aneurysms, supports a radical surgical approach to the treatment of non-ruptured aneurysms. In every patient in whom rupture had occurred, pain in the abdomen and back was present, as well as a palpable pulsating mass. In fact, in twenty-nine the outstanding physical finding was the presence of a pulsating mass in either the right or left flank, the latter being predominant. Shock as a result of blood loss was present in fourteen, and evidence of blood loss was present, in the form of a lowered hematocrit, in twenty.

The location of the rupture in each of the thirty-two patients is shown in Table II. The opportunity to operate on a patient not in shock after rupture of the abdominal aortic aneurysm appeared to be best in those instances in which the rupture took place into the retroperitoneal space where containment of the extravasated blood in a pulsating hematoma is most likely to occur. In twenty-eight patients having this location of rupture, there was a mortality of 50 per cent, while in three patients in whom rupture occurred into the gastrointestinal tract, the mortality was 100 per cent. Rapid death from the latter route of rupture was not encountered, but death in each instance was due to infection of the implanted graft and rupture of either the graft or of a suture line. One patient with rupture into the inferior vena cava (noted in Table I) was operated upon approximately ten hours after the onset of the first symptom. Two hours prior to resection, massive edema of the lower extremities rapidly occurred. At the time of surgery, the aneurysm was found to have ruptured into the inferior vena cava and into the retroperitoneal space. Resection of the lesion and Dacron graft replacement, combined with excision of the vena cava, necessitated by the damage to this vessel, produced satisfactory results, including immediate resolution of the edema of the lower extremities.

Diagnosis of a non-ruptured abdominal aortic aneurysm depends on the physical findings, which are usually unmistakable, and the roentgenographic picture, which often shows a characteristic calcified aneurysmal wall. The mistaken diagnosis of aneurysm is occasionally made. In the present series this occurred in four patients. Two of these exhibited large, midline disc-shaped kidneys lying on the aorta in such a manner as to transmit the aortic pulsation to the palpating hand. One patient was found to have a primary carcinoma of the pancreas, while the fourth had a metastatic tumor, with the primary originating in a very small seminoma of the testicle.

CLINICAL COURSE AND MORTALITY

Ninety-six patients with non-ruptured abdominal aortic aneurysm have been followed-up in this series for a period of from six months to seven and a half years. In this series fifty-seven of the patients had no complaints. Pain was present in thirty-nine. Intermittent claudication was complained of by twenty patients. Weight loss and gastrointestinal disturbances were often present.

Whereas the mortality which resulted from resection of ruptured aneurysm was overwhelmingly governed by the presence or absence of shock on admission to the hospital, the mortality in the non-ruptured group can be principally related to the presence or absence of symptoms arising from the presence of the aneurysm

TABLE III
Mortality in Surgery of Abdominal Aneurysms

Type	Patients (no.)	Died (no.)	Rate (%)
Asymptomatic	57	4	7
Symptomatic (non-ruptured)	39	9	24
Ruptured	32	17	50
In shock on admission	14	10	77
No evidence of shock	18	7	39

(Table III). The over-all mortality in ruptured aneurysms was 50 per cent. In patients in shock on admission the resection mortality was 77 per cent, while in eighteen patients with ruptured aneurysms who were in stable condition on admission the mortality was 39 per cent. Asymptomatic non-ruptured aneurysms were resected with a mortality of 7 per cent, while those having symptoms from their aneurysm suffered a mortality of 24 per cent.

Selection of Graft Material for Aortic Bifurcation Replacement

Replacements of the aortic bifurcation or bypass of the bifurcation which can be completed entirely within the abdomen do not provide a critical test of graft materials. The size of the vessels involved and the consequent diameters of the prostheses which may be used strongly support the long time function of the graft as a blood-carrying structure. It is, of course, important that the vascular wall provided by a homologous artery graft or a prosthesis retain its intrinsic strength permanently.

Although cases of unsatisfactory behavior of homologous grafts have been reported by others, our own series, which includes ninety-seven homologous artery replacements, has shown only four true graft failures. Three consisted of rupture of the homologous artery within the first week after implantation. In each instance the graft had been prepared by freeze-drying after sterilization by immersion in betapropriolactone. Thereafter, until the use of homologous grafts for aortic bifurcation was discontinued, only ethylene oxide was used for their sterilization.

Almost any long-lasting non-reactive permeable prosthetic material appears suitable for replacements confined to the bifurcation. However, extension of the bypass down to the popliteal artery level, made necessary by severe disease in the superficial femoral arteries, requires carefully selected prosthetic materials.

In the work reported in this series, a closely woven taffeta Dacron bifurcation produced in a variety of sizes has been used. This prosthesis which was jointly developed and tested in our laboratory and by Deterling of New York,[5,6] is crimped by the application of heat, giving it an unusual longitudinal elasticity and resistance to kinking in passage of the hip and knee joints. When extension of the graft to the popliteal level is necessary, a crimped tube of the same material is sutured to the limbs of the graft, passed under Poupart's ligament and through the adductor canal, finally being anastomosed end-to-side to the popliteal artery. Extension of an aortic bifurcation graft to the femoral level was necessary in thirty-six patients with occlusive disease and extension to the popliteal level was required in thirteen. The success rate in these two areas are thirty-one (87 per cent) in the former and twelve (93 per cent) in the latter.

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Surgical Treatment of Femoropopliteal Arterial Occlusive Disease*

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In summarizing the concepts I have followed in my approach to the surgical management of femoropopliteal arterial occlusive disease, the opinions expressed will perhaps be colored by some personal preferences. However, the ideas conveyed will not be significantly different from those generally current among surgeons interested in vascular surgery. For, after a period of great instability, vascular surgery has now reached a phase in its brief history where ideas and methods are, while not standardized, fairly uniform.

For the sake of clarity it will be well at the outset to define the term "arterial occlusive disease." This designation is practically synonymous with arteriosclerosis obliterans, but it is preferred because of its intentional vagueness. The name "arteriosclerosis" is closely associated with the pathologic picture of medial sclerosis, while atherosclerosis denotes a clearly defined specific morbid change. The lesions with which the clinician deals, on the other hand, represent combinations of both these pathologic processes in varying states of advancement. These conglomerate lesions are more truthfully described by the term "occlusive disease" which stresses the clinically important unitary end result of the multiple and diverse pathologic changes. In order to avoid misunderstanding with regard to "Buerger's disease," whenever reference is made to this entity, its full name will be given.

Pathologic Anatomy

Peripheral occlusive arteriopathy has become a surgical disease only during the past decade. This change of status has come about through recognition, mainly by the use of clinical angiography,[1] of the essentially segmental character of the pathologic processes leading to stenosing and occlusive arterial lesions. Arteriosclerosis is, of course, a systemic disease, but its manifestations of greatest clinical importance are segmentally localized. Some degree of intimal, and to a lesser degree medial, alteration is present in practically all the large and medium-sized arteries of the patient with clinical evidence of arteriosclerosis, regardless of the localization of the clinical manifestations. At certain points in the arterial tree, however, these changes are markedly more accentuated.

In terms of pathogenesis, the systemically operative factors—metabolic, hormonal and hereditary—bring forth the fundamental and diffuse alterations, while local factors—mechanical stress, anatomic features and hemodynamic peculiarities lead to the segmental accentuation of the occlusive process. When this process in a given involved segment becomes complete (the last event being usually one of thrombosis), the arterial trunk both upstream and downstream from the initial point will become obliterated by clotting; the thrombosis extends in both directions to the site of origin of the next proximal and distal branch of sufficient size to provide, respectively, adequate outflow and inflow. The length of the segment put out of function by the occlusive-thrombotic process will depend on individual anatomic variations (i.e., the distance to the next available arterial branch) and on the state of pathologic involvement of the potential collateral arterial tree. In any case, with the progress of the systemic process, newer segments may become obliterated, and in fact, by a process of coupling, practically the entire major arterial trunk system of an extremity may become obstructed. Thus, the originally segmental occlusive process may become diffuse.

In the simplest terms, the clearly segmental type of occlusive arterial disease may be called *early*, and the diffuse type, *late* or *advanced* clinical manifestations. In actual surgical practice, however, the picture is more complex. In

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some patients segmental lesions seem to persist without much advancement for long periods of time (at least as long as five years), while in others the first serious clinical findings appear only when the pathologic process is already quite widespread.

In general, the obliterative process in clinical practice tends to be diffuse, or more precisely, multiple. Nevertheless, the distinction between the purely segmental and the diffusely widespread types of disease is a useful practical concept. This usefulness is evident when one considers either clinical symptomatology or surgical management.

Symptomatology and Diagnosis

In segmental (or, if one prefers, in the early forms of) occlusive disease there is an ample collateral arterial bed available to carry enough blood around the obstruction to supply the tissue needs at rest. On exercise, however, the need of the muscles for oxygen is multiplied manyfold and the collateral blood flow is seldom sufficient to meet it. With great regularity in this type of occlusive disease, the patient is symptom-free at rest, but complains of ischemic pain in the muscle mass most heavily involved in physical effort and lying distal to the level of obstruction (in the case of femoral arterial occlusion, in the calf muscles). *In the diffuse type of involvement* (which may also be termed the *advanced form* of this disease), the collateral arterial branches are so meager that adequate blood flow cannot be carried to the musculature or indeed to the distal portion of the extremity. Pain at rest will be common and the foot will show the evidences of severe ischemia at rest (cyanosis, pallor and dependent rubor). Eventually, of course, actual death of tissue will occur.

It is the type of disease with the occlusive lesions still limited to relatively short segments which is suitable for surgical correction. In these cases, as a rule, there will be proximal and distal arterial segments that allow good potential inflow and, in case of grafting, satisfactory vascular trunks on which to affix a prosthetic implant. In the diffuse form of disease these necessary conditions do not exist, and the surgeon cannot offer help by angioplastic operations. The singularly attractive feature of reconstructive arterial surgery is its ability, under the conditions just mentioned, to restore an arterial circuit to the state of function it possessed before the development of the occlusive lesion. To this extent an open arterial graft is a dramatic and unequivocal therapeutic success that no other form of treatment for occlusive disease can even approach. (Needless to say, the permanence of the results is a different matter, a subject which will be touched upon presently.)

Diagnosis: The extreme forms of the two types of clinical manifestation can be diagnosed with great accuracy without laboratory aid. A limb that appears normal to inspection and functions well except when called upon to perform rather strenuous exercise is the seat of the segmental (or early) form of the disease; the absence of pulses will confirm the diagnosis and also localize the level of the block. The limb with atrophic skin, and a dusky, cold foot that turns fiery red in a dependent position and is painful at rest is obviously involved in a diffuse (and advanced) type of arterial occlusive disease. In between, however, there are many transitional degrees of disease in which clinical judgment cannot measure the extent of the process, and therefore a decision regarding operability cannot be made on such a basis alone.

Peripheral Angiography

Of greatest importance to the surgeon in determining whether or not an operative procedure is indicated is angiography. Indeed, after some trials with other diagnostic technics, such as plethysmography and oscillometry, I have come to the conclusion that, for the purposes of determining prognosis, progression and operability, angiography alone possesses the reliability and accuracy to make it a practical clinical tool, and hence I use no other diagnostic aid.

In our practice peripheral angiography is virtually identical with translumbar aortography, since the visualization of the arterial tree from the level of the renal arteries to the level of the popliteal arterial branches is practically always obtained through a translumbar aortic puncture. Percutaneous femoral arteriograms are seldom recorded.

When properly performed, angiography offers the unexcelled advantage of a veritable blueprint of the arterial tree. In an angiogram of satisfactory quality the surgeon can decipher not only the type and extent of the obstructive lesion but he can also determine the state of involvement of the adjacent proximal and distal arterial beds and judge the adequacy of arterial inflow and outflow, indispensable information for the rational planning of the operative procedure. The value and usefulness of angiog-

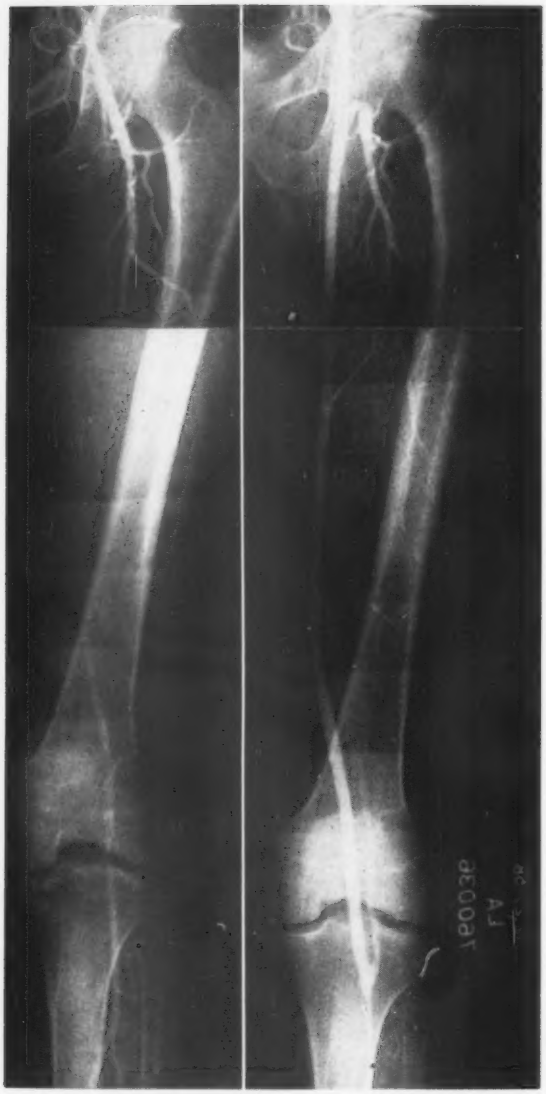

FIG. 1. Preoperative femoral arteriogram (*left*) in a patient in whom the only symptom was incapacitating intermittent claudication in the calf muscles (group I). The occluded portion of the superficial femoral artery is well demarcated and is bordered by relatively unaffected arterial segments. *Right*, Good operative result.

raphy, however, are importantly qualified by the circumstances under which it is performed. The basic concepts of this procedure (the acquisition of a radiogram after the intra-arterial introduction of the appropriate contrast medium) are deceptively simple, but without the faithful observance of certain precautions, the exercise of some skill and the use of suitable equipment, this method of examination may become not only diagnostically unreliable but also unacceptably risky. All the diagnostically useless angiograms we have seen and virtually all the serious mishaps following angiographic examination with which we have been acquainted resulted from the violation of these simple precepts.

Indications: As a first principle of safety, aortography should not be recommended as a purely diagnostic examination, but should be conceived as a study aimed at determining operability. There is no justification, for instance, for obtaining angiograms in cases of occlusive arterial disease in which the clinical findings clearly show changes beyond the possibility of surgical correction. Likewise, angiography is seldom indicated in instances in which the presence of occlusive arterial disease can be ruled out with reasonable certainty using clinical means, or when the symptoms, although typical of obliterative disease, are not severe enough to warrant the consideration of surgical treatment. There are some cases of difficult clinical symptomatology in which resort to angiography as a purely diagnostic tool is warranted, but their number is exceedingly small.

Technic: With regard to the actual performance of the examination, we have come to regard it as a major operation, with all the safeguards obligatory for such a procedure. The patient is hospitalized for forty-eight hours, subjected to a complete physical examination, and his cardiac and renal status is checked by means of electrocardiography and a simple renal function test (usually the serum creatinine level). The examination is performed under general anesthesia, and the operator is one who has had thorough instruction in the technic and has performed at least 50 aortic injections under supervision. The contrast medium used is that which has proved the safest from the point of view of systemic reaction, and it is given in the minimum amount compatible with satisfactory opacification (at present, 25 cc. of 70 per cent Hypaque®); the patient is tested for hypersensitivity before administration.

Whenever at least one femoral arterial pulse is present, a low aortic puncture (about 4 cm. above the bifurcation of the aorta) is used in order to reduce the amount of dye reaching the kidneys. Before introducing the full amount of contrast medium the position of the aortic needle is ascertained with the help of a scout film obtained after the injection of 2 to 3 cc. of the contrast medium. In order to minimize the need for repeated injections, the most common cause of which is improper timing of the

exposure, a casette changer is used that can take 36 by 17 inch films and can make seven sequential exposures in ten seconds. If satisfactory films are not obtained, which is quite uncommon, the injection is repeated only if it appears safe; otherwise the examination is carried out again on another day. In some instances of questionable risk, with good femoral pulsations present, precutaneous femoral arteriography is used in preference to aortography.

The aforementioned angiographic routine has proved quite safe. In over 1,500 angiographic examinations we observed only two serious (but non-fatal) complications.

Operative Indications and Contraindications

While the decision regarding operability is made from the angiographic findings, the results of the clinical examination are nevertheless all important since the primary selection of the cases, i.e., the decision whether or not angiographic studies should be carried out, depends on these. The clinical picture obtained from history and physical examination, on the basis of which the surgeon chooses his further course, generally falls into one of four categories that broadly correspond to the pathologic variants already outlined.

Group I: The first and largest group comprises patients with intermittent claudication, no rest pain, and, aside from absent pulses, a grossly normal limb (Fig. 1). The thorny problem in this group is the determination of the urgency for operative treatment. An angiographic survey is recommended in all patients except those with trivial symptoms, for even if surgical treatment is eventually not chosen, the angiographic visualization of the obstructive lesion renders further follow-up much more intelligent. Moreover, not infrequently, the extent of the disease is more menacing than the clinical symptoms would suggest. The evaluation of the need for surgical treatment, however, is made primarily on the grounds of the degree of disability. If the discomfort on exercise is not severe enough to interfere with the patient's livelihood or normal mode of living, operative treatment is not advised. Making the operative selection primarily on the strength of the angiographic appearances will lead to some meddlesome interventions. This error is an easy one to commit because these cases present the largest proportion of technical favorable, sharply localized lesions.

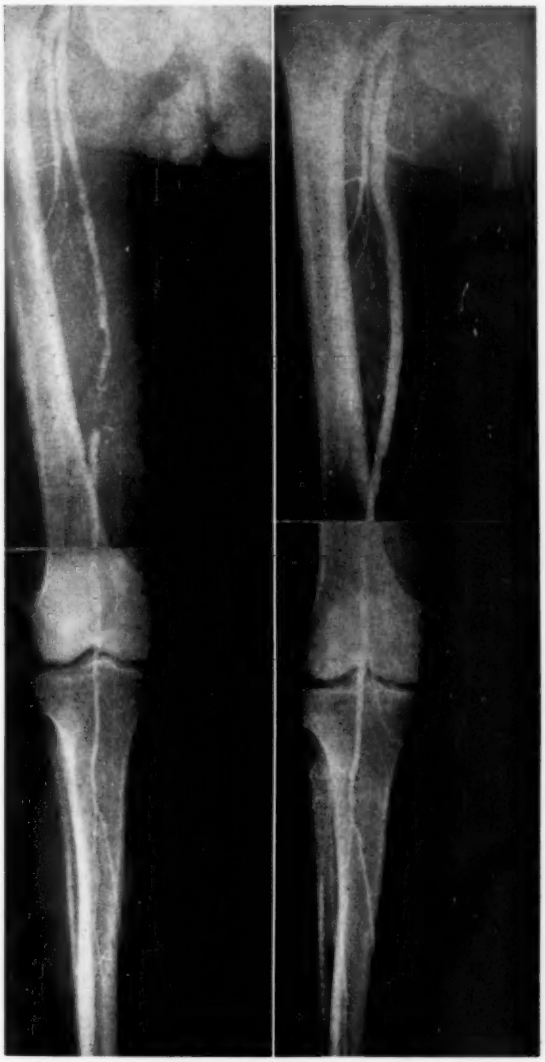

Fig. 2. Preoperative femoral arteriogram (*left*) of a patient with sudden onset of ischemia following a period of mild intermittent claudication (group II). A sharply localized occlusion of the superficial femoral artery is demonstrated, with poorly developed collaterals. Clinically the foot appeared to progress rapidly toward gangrene. A graft (*right*) corrected the occlusion, and good recovery followed.

Group II: The second, third and fourth groups have the feature of rest pain in common. The patients in the second group have a history of sudden onset of severe ischemia, including rest pain and pregangrenous skin changes, that supervened after a period of intermittent claudication of varying severity (Fig. 2). Pathologically, the underlying changes are those of a fairly well localized segmental occlusive process, with a superimposed sudden terminal thrombosis and

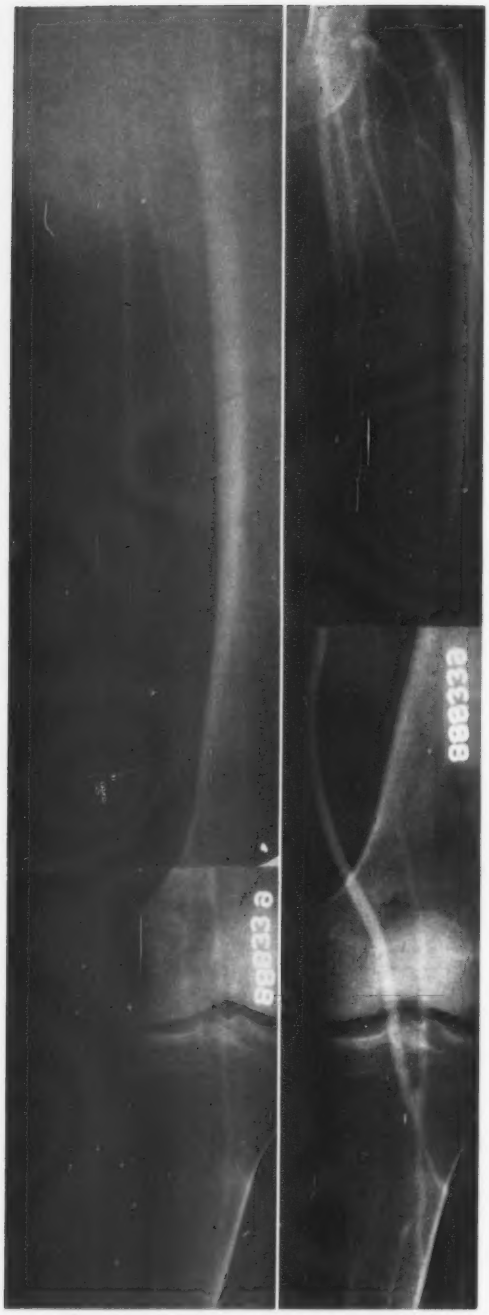

FIG. 3. Preoperative femoral arteriogram (*left*) of a patient complaining of incapacitating intermittent claudication and mild rest pain (group III). The occlusive lesion of the superficial femoral artery is well demarcated and there is an open distal segment but the branches of the popliteal artery show disseminated stenoses. Successful femoropopliteal bypass graft (*right*) of elastic Dacron.

without adequate immediately available collateral circulation. The appearance of the affected limb usually suggests rapidly developing gangrene, and if the obstruction is not corrected, either because of delay or because of technical reasons, irreversible gangrene will, in fact, ensue. The important historic clue in the clinical picture is the suddenness of the onset of the severe ischemia.

A femoral angiogram should be obtained, and in about half the cases an occlusion will be found in the lower femoral level (commonly in the area of the adductor hiatus), with an open popliteal segment; if this is the case, a grafting procedure will usually correct the obstruction. Unfortunately, in the other half of the cases the occluding lesion is close to, or at the point of, division of the popliteal artery and an angioplastic operation is technically impossible.

Group III: The third clinical group includes the second largest class of patients under discussion (Fig. 3). The history is relatively long, at first consisting of intermittent claudication. There is a recent onset of rest pain which is not severe. The visible signs of tissue ischemia at rest are mild or moderate. The angiographic findings show diffuse involvement, particularly as regards the branches of the popliteal artery, but with a patent popliteal segment that is often suitable for anastomosis. Not infrequently this type of femoropopliteal involvement is associated with occlusive lesions in the aortoiliac area; in fact, the higher lesion may be the more important factor in producing the clinical symptoms and signs.

This is the group of patients in whom evaluation of the angiographic findings for the proper surgical approach is of the greatest importance. It is essential, for instance, to assess carefully the state of the aortoiliac segment, for if it is also involved an attempt to correct the more distal lesion (in the femoropopliteal region) first will generally fail. Conversely, the reconstruction of the aortoiliac segment may often bring about enough improvement to make an operation for the femoral disease less urgent or even unnecessary. Unfortunately, the angiographic appearances are often on the borderline between operability and inoperability. The decision with regard to which course to follow will then depend on the judgment of the surgeon, and here there is room for a variety of opinions. In some cases, moreover, the images seen in the roentgenograms may be misleading and at exploration the arterial lesion may prove non-correctable. (It may be mentioned here that in general the occlusive process as found at

operation is more advanced than the picture suggested by the angiograms.)

Group IV: The fourth clinical group gives the least cause for the exercise of judgment or skill. Patients included here have long standing, slowly progressing disease with established gangrene by the time they seek medical advice (Fig. 4). Experience has proved that even angiographic exploration is unwarranted in these cases, and the only surgical help to be offered is amputation.

Other Contraindications to Surgery: In regard to operative contraindications not primarily concerned with the degree of the local occlusive process, an important instance in which angioplastic operation is frequently ill advised is one in which the patient, in addition to symptomatic peripheral arterial occlusive disease, has severe coronary arteriosclerosis. In this situation one faces the danger of supplying the patient with the means of aggravating his potentiality for myocardial infarction by allowing him to exercise more vigorously. Fatal results from increased activity following successful peripheral angioplastic operations have occurred in my experience in patients with arteriosclerotic heart disease operated on for intermittent claudication. The problem is quite different, of course, when there is evidence of impending gangrene or severe rest pain; here operation is mandatory. In this same general category, I do not operate on patients with severe residuals of the organ manifestations of arteriosclerosis, such as cerebrovascular or renal arteriosclerosis.

Selection of Patients: Using these principles of selection, among 444 patients seen between September 1, 1956 and August 31, 1958, angiograms were recommended in 415 (or 93.0 per cent) for the evaluation of operability; the other 29 (or 7.0 per cent) were either free from occlusive arterial disease or clinically judged inoperable. Of the patients on whom angiograms were performed, 244 (or 59 per cent) were found to be suitable for surgical exploration. After this was carried out an angioplastic operation was performed in all but six of these. Of the original 444 patients, therefore, 58 per cent actually underwent a reconstructive surgical procedure.

FIG. 4. Femoral arteriogram of a patient with advanced, disseminated occlusive lesions (group IV). There is no popliteal arterial segment suitable for anastomosis. The collateral circulation is adequate enough to prevent gangrene, but the patient complained of severe ischemia at rest.

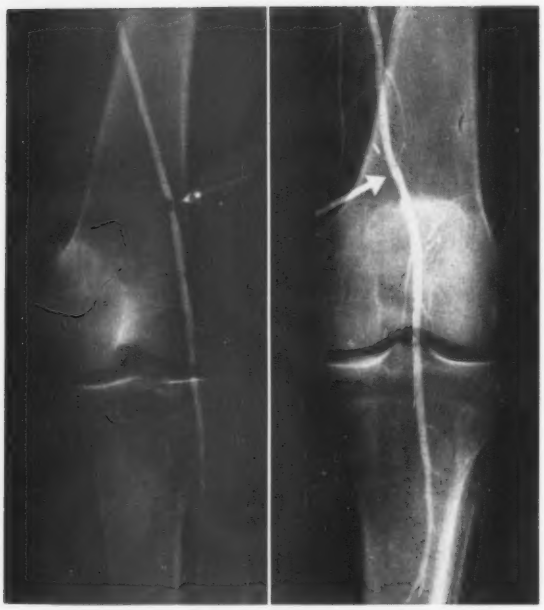

FIG. 5. Narrow occluding lesion of the popliteal artery (*left*). Although the occlusion was not quite complete, the patient had marked intermittent claudication which was relieved by endarteriectomy (*right*).

CHOICE OF OPERATIVE PROCEDURES

The surgeon has two technics at his disposal in planning the correction of an arterial occlusive lesion: thromboendarteriectomy and grafting.

Thromboendarteriectomy[2,3] is considerably the older operation, having been in clinical use for about fifteen years. It consists of removing by sharp dissection the occluding plug from the arterial lumen, i.e., the central thrombus with the thickened intima and the diseased inner portion of the media adherent to the intima. A ready cleavage line is almost always found and the obstructing tissue separates cleanly, leaving a smooth arterial wall that is only about one-third to one-half its normal thickness but still strong enough to maintain its mechanical integrity. Eventually a new intima is formed over the luminal surface which is largely organized fibrin but may at least in part be true regenerated endothelium. Because of the remarkable degree of regeneration of the luminal surface of the artery, the end result of endarteriectomy is physiologically most satisfactory. In this sense such a procedure is superior to grafting which, with very few exceptions, involves the insertion of a foreign body into human tissues. Unfortunately, when thromboendarteriectomy is applied in the treatment of occlusive disease of the smaller arteries, i.e., femoropopliteal arterial disease, the problem of preventing thrombosis of the dissected segment, unless it is of relatively short length, creates serious practical postoperative difficulties. Moreover, the operation on long segments of the smaller arteries is most demanding in time and skill. When the many requirements necessary for success are not religiously observed, the failure rate with this operation is high.

Because of these considerations, and since the early success rates even in the best series reported are not significantly different from those obtained in comparable cases treated with grafting procedures, I have used thromboendarteriectomy only in about 4 per cent of my patients with femoropopliteal occlusive disease. While I resort to this technic in the treatment of aortoiliac involvement whenever conditions permit, it is reserved for those femoropopliteal lesions in which the affected segment is 5 cm. or less in length and is bordered by grossly normal tissues (Fig. 5), a practice which is fairly universal.

Grafting Procedures: By far the most commonly used surgical technic in the treatment of femoropopliteal occlusive lesions is grafting[4,5] (Fig. 6).

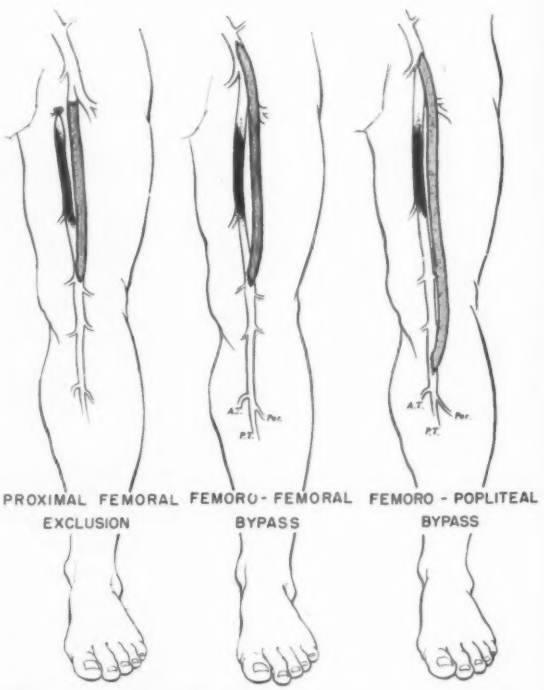

FIG. 6. Frequently used variations of angioplastic technic in the femoropopliteal area.

Although it has been in wide acceptance for less than ten years, this procedure has undergone a number of technical changes. Arterial grafting originally meant *arterial replacement*, i.e., the freeing of the diseased arterial trunk, its removal, and its substitution with end-to-end anastomoses by a new vascular channel, either a homologous artery or an autogenous or homologous vein. The lack of need for the removal of the affected segment soon became evident, and exclusion operations were evolved.

At present, *bypass grafting*[6] is the technic used in most situations, and without any important exceptions in all femoral arterial occlusions. In this procedure the diseased arterial segment is left undisturbed and not even dissected out; the graft is inserted by end-to-side anastomosis to the host artery both above and below the diseased segment. The method has the great advantage of being a lesser operative trauma and leaving all the important remaining collateral arterial branches entirely untouched. Hemodynamically the operation appears to be about as effective as direct replacement with end-to-end anastomosis. The operation can be employed in the management of most reconstructive problems from the carotid region to the aortoiliac and femoropopliteal areas.

The placement of femoral bypass grafts has for long been from the groin to just above the knee region, a technic that circumvents most but not all the occlusive process encountered in the thigh. Through this approach in the thigh, lesions lying in the distal femoral area or in the popliteal trunk cannot be corrected. More importantly, if the distal reach of the bypass graft is limited to the thigh even in instances in which the segment of the femoral artery bearing the occluding lesions is completely bridged, segments of this vessel further distalward, often involved in the stenosing process although still open, are left uncorrected. Follow-up angiographic studies have indeed shown that the progression of the disease in the distal portion often leads to late failure of the operation.

For the aforementioned reasons I have turned to the use of a *long femoropopliteal bypass*[7] in all cases of operable femoral or femoropopliteal occlusive disease. The graft in this operation extends from the external iliac or common femoral artery to the distal popliteal artery, the anastomosis being made through anteromedial incisions without changing the position of the limb (Figs. 7 and 8).

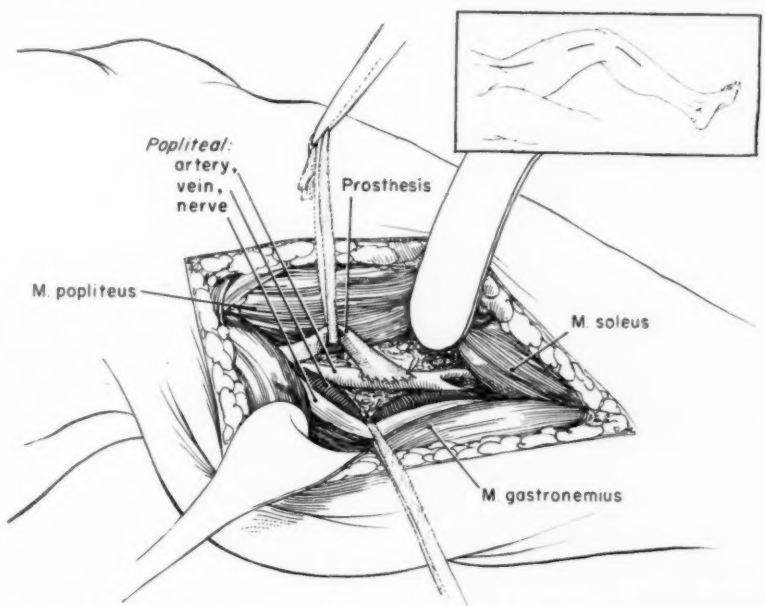

Fig. 7. Exposure for popliteal anastomosis. The essential features of a femoropopliteal bypass graft. The approach is through anteromedial incisions in the thigh and in the upper tibial region, without change of position of the limb. The details of the tibial dissection are shown. The path of the prosthetic implant from the groin to the calf follows closely the anatomic course of the femoropopliteal arterial trunk.

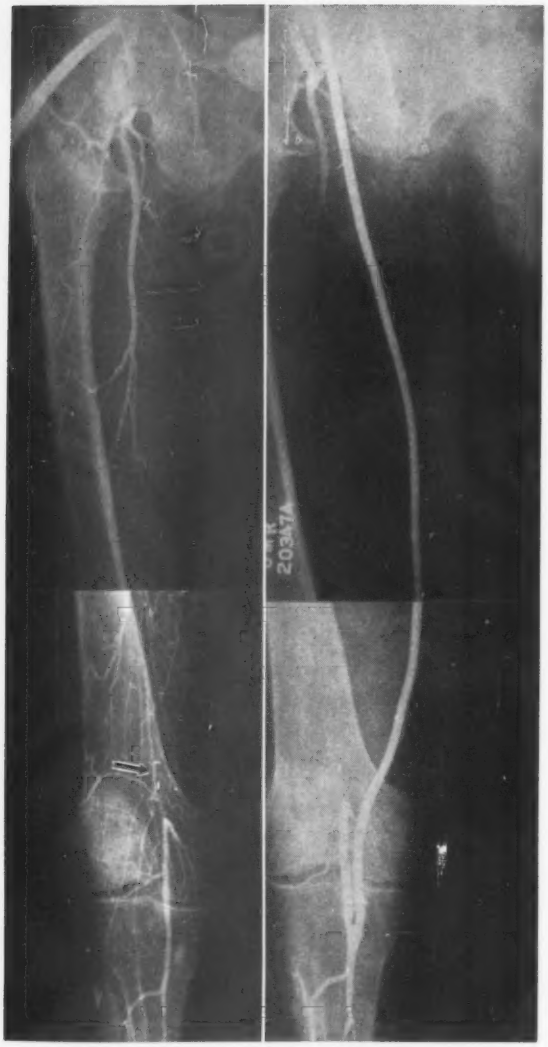

FIG. 8. The preoperative (*left*) and postoperative (*right*) femoral arteriograms in a case in which a precise femorofemoral operation had failed because of the progression of the occlusive process in the distal femoral region. (Arrow points to the site of the previous distal anastomosis.)

At times this operation may be combined with an *aortofemoral bypass*, thus bridging the arterial disease from the level of the abdominal aorta to the level of the point of division of the popliteal artery.

CHOICE OF ARTERIAL SUBSTITUTES

Arterial Homografts: Until about three years ago the surgeon had small cause for concern about the type of arterial substitute he was to use for a grafting operation. The view was generally accepted that a well processed homologous arterial graft not only looked and behaved like the patient's own healthy artery but that it also would continue to function indefinitely in the manner of a normal vessel. Except for the problems of obtaining and processing them, which were considerable, arterial homografts appeared to be the ideal substitutes. Unfortunately, when critical follow-up observations began to be gathered on those implanted two years or longer, it became evident that their lasting quality was unsatisfactory.

Histologic studies[8] have shown that arterial homografts are not actively accepted and incorporated but only passively tolerated and at times even rejected by the host. Furthermore, they maintain their structural integrity only through the mechanical strength inherent in their histologic elements. When these wear out, as they inevitably do in time, the wall of the graft weakens, becomes dilated and is eventually occluded by thrombosis; rarely it ruptures. Since the histologic elements essential for mechanical integrity are the elastic laminae, in aortic grafts, extremely rich in elastic components, the process of wearing out may take many years; indeed, in most cases the graft outlives the patient. Femoral grafts, on the contrary, being very poor in elastic tissue and consisting mostly of smooth muscle and collagen fibers, show structural failure relatively early and in a high incidence. These observations have largely invalidated the clinical usefulness of arterial homografts. Therefore, in spite of their versatility, ease of technical handling and excellent early success rate, the use of these substitutes has been given up gradually.

Plastic Substitutes: Aside from the recognition of their intrinsic deficiency which made their obsolescence inevitable, the passing of arterial homografts was hastened by the emergence of arterial substitutes constructed of woven yarn of plastic materials of diverse types. Investigation of these prostheses had, in fact, begun, mostly for reasons of convenience, even before the inadequacy of homografts was established, following the pioneering observation of Voorhees and his associates,[9] reported in 1952, that the animal body builds a connective tissue channel around a porous textile fabric placed in the path of the flowing blood. The awareness of the lack of permanence in the structural strength of arterial homografts lent further urgency to this search, and as a result a number of plastic

substitutes have been put to clinical use, at least four of which have gained a popularity of some degree. Indeed, at present the surgeon's dilemma is not how to come by a graft (as it was in the days of the use of homografts) but which of the available ones to choose.

Instead of attempting to pass judgment on the comparative merits of the plastic arterial substitutes now in use (which neither the scope of this essay, nor, for that matter, the recorded experimental and clinical information permits), I shall describe briefly the qualities that by fairly universal agreement a plastic prosthesis must possess to be suitable for wide range clinical use,[10] with occasional references in general terms to ways in which these requirements have been met by the various available substitutes.

REQUIREMENTS OF GOOD PLASTIC PROSTHESIS

Durability and Lack of Tissue Reactivity: The first requirement is concerned with the nature of the plastic of which the fibers, the fundamental unit of the fabric, are composed. In this regard the qualities sought are durability and the lack of excessive tissue reactivity, that is, the lack of excitation by the plastic of an excessive inflammatory exudate in the tissue environment. Of the three most widely studied plastics—nylon, Dacron® and Teflon®—nylon has been abandoned due to its rapid loss of tensile strength after implantation. Dacron and Teflon stand close together in regard to the two essential qualities mentioned. In animal experiments Teflon shows almost complete lack of tissue reactivity; in fact, it is my impression that such a response has a somewhat undesirable effect on the completeness of the incorporation of Teflon tubes. Dacron is only slightly more reactive. It is assumed by some that in terms of long follow-up observations, Teflon, which is so exceptionally inert, will prove more durable than Dacron. Up to two years, however, my experimental observation has clearly shown that Dacron remains practically unchanged with regard to its tensile strength.

Porosity: A most important requirement is porosity. It has been shown beyond doubt that non-porous tubes, regardless of construction or the nature of the component material, will not function as arterial substitutes. Crevices in the wall serve as starting points for the deposition of a thin fibrin layer on the inner surface that eventually is organized into a lining, in the ideal case, closely resembling an arterial endothelium. They also act as sites of entrance and anchorage for the connective tissue that gradually envelopes the implanted tube.

The size and density of the pores are critical factors. Pores of too large size cause excessive bleeding before they are sealed by fibrin plugs; in fact, in the extreme they may not be sealed at all. Pores too densely placed interfere with the process of arteriogenesis—the ingrowth of connective tissue and the formation of pseudointima—and may create physical conditions approximating those in a solid prosthetic tube. All currently used prostheses are porous by virtue of their construction as textile fabrics, either woven knitted or braided. There is good histologic evidence suggesting that a simple taffeta weave (which is the pattern of weaving in most ordinary shirting materials) has advantages over the other types, the chief of which is the orderliness with which arteriogenesis proceeds on the simple geometric trellis such a textile pattern offers.

Flexibility and Elasticity: A further important quality is the ability of the prosthesis to elongate and recoil. This property must be present owing to the necessity for the prosthesis to accommodate itself to the anatomic features of its surroundings. When curved or flexed, a rigid tube will buckle and wrinkle, and this in turn leads to clotting. Flexibility in a prosthesis has been achieved by various means: by using a knitted fabric, by crimping the tube or by incorporating longitudinal yarns with elastic quality ("Helenca®" yarn). These variations of construction produce excellent flexibility, but crimping and knitting, by creating irregular and rough surfaces, interfere with blood flow. In addition, a knit pattern tends to decrease durability through the unequal distribution of stress in the fabric; knitted fabrics also increase bulk. Both Dacron and Teflon can be crimped, but the Helenca process of elasticising the fibers cannot be applied to Teflon. The intrinsically elastic prostheses available at present are made of Dacron.

Other Qualities: As regards certain minor qualities, which, however, have a good deal of practical significance, all presently used plastic prostheses are reasonably inexpensive and are easy to store and sterilize. From the point of view of ease of handling, Dacron fabrics can be sutured with somewhat greater facility than Teflon. For safe use, all porous fabrics

must be preclotted, i.e., before insertion, blood must be rinsed through the tube to allow the formation of fibrin plugs in the pores. Knitted fabrics have the advantage of being able to be trimmed without the need of heat-sealing the cut edges; in woven fabrics the edges must be melted with a cautery blade to prevent unraveling of the yarn in course of suturing.

At the moment the preference for one or another of these substitutes is usually decided on grounds of minor advantages. In the long range view, the future belongs to the prosthesis that will combine the most nearly perfect arteriogenesis with the greatest durability. Only long and critical observation will yield this choice.

The Value of Angioplastic Operations

Any assessment of the results of reconstructive operations for peripheral arterial occlusive disease must be introduced by the statement of some facts that are obvious but often forgotten: (1) Until the emergence of these surgical procedures, there was no effective method of influencing in a significant way most of the disabling and crippling manifestations of peripheral arteriosclerosis. (2) It would be a conspicuous mistake to speak of cure in connection with an operation that attacks only one phase—and often not a major phase—of a systemic disease that is not only incurable but also cannot be arrested. (3) If the previous two circumstances are kept in mind, the value of angioplastic operations must be expressed as the balance between the periods of disability relieved and prolongation in the life of a limb gained on the one hand, and the lives and limbs prematurely lost because of the operative attempt on the other. Unfortunately, such a balance in exact statistical terms has not yet been reported, and, insofar as our own experience is concerned, cannot as yet be made, since the relevant clinical material for analysis in the desired numbers and with the necessary follow-up period is just becoming available. Any judgment in this regard is at present to some degree a subjective impression.

Early and Late Results of Surgery: With respect to the results of the surgical operations for femoropopliteal occlusive disease, one fact has been clearly established. They are much less satisfactory than those obtained in the aortoiliac area as regards both early and late figures. Whereas in the treatment of aortoiliac disease I have observed an early success rate (i.e., patent, well functioning grafts up to two years postoperatively) of 85 per cent, in the femoropopliteal area the average early patency rate is only 70 per cent. Moreover, until two years ago (when the use of homografts was completely abandoned) a progressive yearly loss of 10 per cent in the patency rate was experienced. In a group of 150 patients of femoropopliteal reconstruction followed up for four years, the patency rate was 35 per cent. During the same time the patency rate in aortoiliac operations had dropped only 10 per cent.

The cause of these late failures was multiple.[11] Some lost their initial good result because of homograft degeneration, and a small group did so owing to technical imperfections. By far the most common cause for deterioration of the results was, however, the progression of the basic disease. At first glance this observation bodes ill for the future, but further analysis of the group shows that in about half of the instances of late failure the progression of the disease occurred in an area that was overlooked at the original operation. This was most commonly seen in the popliteal region, an anatomic area that until recently was not accessible to a convenient surgical approach. There is a good reason to expect that with the more complete circumvention of the popliteal disease (as previously described), this source of late failures will be eliminated. Likewise, one can hardly doubt that beyond the second postoperative year the use of plastic prostheses will improve the results. If past experience can be projected into the future, on the basis of the improvements now at the surgeon's disposal, a 70 per cent two-year cure and 50 or 60 per cent five-year cure seem to be reasonable expectations, assuming that the operative indications remain the same.

Several considerations suggest that this is an entirely acceptable therapeutic reward. The mortality of angioplastic operations on the femoropopliteal arterial trunk is very low, in my series less than 1 per cent. It is difficult to say how many limbs were made worse by unsuccessful operative intervention. However, it can be stated with certainty that: (1), in cases in which aggravation of the state of the limb would have been most regrettable (i.e., in instances of pure intermittent claudication), this type of misfortune is practically never observed, and (2), in virtually every case requiring amputation after an unsuccessful attempt at reconstruction, eventual removal of

the limb was only a question of time. True, in the last-named group the life of the limb was shortened in a number of patients. This class of patients, however, is far outnumbered by those whose seemingly inevitable amputation was prevented not perhaps forever, but for many valuable years.

In discussing the results of angioplastic operations, one other fact must be mentioned. It is not difficult for the surgeon to improve his rate of success by restricting his case selection. Indeed, it is his agonizing dilemma whether or not to undertake the wearying job of a reconstructive operation in many cases that look almost hopeless but that need his help most, or rather to take the easy course and refuse operation. It is my belief that avoiding the disappointment of failure in the cases of the severest disease is not the right way to improve the results of these surgical efforts. As long as he is reasonably sure that he may help and that he imposes no unjustified risk of the life of his patient, the surgeon must try.

Thromboangiitis Obliterans

The angiographic investigation of almost all clinical cases of peripheral arterial occlusive disease has brought about a rather surprising and important change in our concept of the incidence of Buerger's disease. A large proportion of cases of occlusive arterial disease that by the earlier standard diagnostic criteria would have been classified as thromboangiitis obliterans have been shown, by angiographic studies, to be instances of arteriosclerosis obliterans occurring in patients in the younger age groups. The error in the former diagnostic criteria was the exaggerated emphasis on the age incidence. Formerly, arteriosclerotic gangrene or pregangrene in a man under forty seemed implausible to most clinicians, while in fact it is not a great rarity. In the early stage the precise diagnosis of Buerger's disease is difficult by any means, but when more advanced and evidences of ischemia are present, the differentiation from arteriosclerosis is usually possible on clinical evidence alone. The combination of severe ischemic pain in the toe or foot at rest, with still patent major arterial trunks (as far distally as the popliteal area) rarely occurs in arteriosclerosis, and then usually in the type associated with diabetes and in older patients.

The angiographic image, when technically good enough to afford adequate visualization of the small arteries of the leg and foot, is a further help in the differentiation. In Buerger's disease it will show a tapering type of narrowing of the tibial and peroneal arteries, fading into complete occlusion as they reach the malleolar and pedal levels. In most instances, however, we prefer to have the diagnosis corroborated by histologic proof. Involving as it does the small arteries in their terminal portions, the occlusion is not suitable for direct surgical intervention and is essentially a non-surgical disease.

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Evaluation of Lumbar Sympathectomy*

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Lumbar sympathectomy is a surgical procedure that is now well established as a valuable adjunct in the treatment of selected cases of peripheral arterial disease. Immediately following World War II there was much enthusiasm for sympathectomy and as a result many patients with peripheral vascular disease underwent this procedure. In the next few years reports indicating a relatively high percentage of poor results were published. With the rapid development of direct operative attack on localized blocks in the peripheral arterial tree, sympathectomy is now assuming its rightful place in the procedures available for treatment. With careful evaluation and selection of patients, a relatively high percentage of good results is obtained. Sympathectomy is a procedure that must be considered as palliative, particularly in peripheral arteriosclerotic vascular disease, because the underlying pathologic process is not influenced by severance of the sympathetic nerves.

Historic Development

The anatomic presence of the sympathetic system was suggested by Galen. Vesalius and Eustachius in the sixteenth century further depicted the anatomy of the nerve trunk and some of the ganglionated plexuses. In the early eighteenth century, Jacque Benigne Winslow used the term "le grand sympathique," because he considered that through these nerves the "sympathies" of the body were controlled.

The physiologic function of the sympathetic nerves was hardly more than guessed at until 1858 when Claude Bernard demonstrated that these nerves controlled vasoconstriction. Further knowledge of the function of the sympathetics was forthcoming from other physiologists.

Adson and Brown observed that lumbar sympathectomy produced vasomotor changes in the lower extremities. In 1925, they carried out a bilateral lumbar sympathectomy on a young patient with Raynaud's disease. Following operation the feet were warm and pink and without vasomotor disturbances. In 1935, Flothow described an anterior extraperitoneal approach which, with some modifications, is still used.

Rationale of Lumbar Sympathectomy

The interruption of the sympathetic system is basically designed to eliminate the mechanism of spasm, which in arterial vessels is a normal physiologic reaction. It is one of the defense mechanisms of the body in which trauma to a vessel invokes vasoconstriction which tends to limit bleeding from the injured blood vessel. This type of spasm, secondary to trauma, is probably mediated directly through sympathetic synapses.

Hormonal production of vasoconstriction is less well substantiated. In animals with shock a substance has been isolated that will cause peripheral vasoconstriction in other animals. The exact nature of this substance is not known, but it may be histamine, as advocated by Bach and others; sympathin, as postulated by White; or an unknown toxin, as suggested by others. It is possible that hypersensitivity to certain materials, such as tobacco, may trigger the reaction. Regardless of the etiology, the efferent fibers causing vasoconstriction are mediated wholly or in part through the sympathetic nerves.

In vasospastic diseases the etiology of the sympathetic overactivity frequently cannot be demonstrated with certainty. However, predisposing or inciting factors, such as cold, emotional stress or associated disease, are usually present. The vessel wall is ordinarily essentially normal. Sympathectomy, by interrupting the efferent pathway, allows more or less continuous vasodilation to take place.

In thromboangiitis obliterans and arteriosclerotic peripheral vascular disease, the trauma from the damaged or occluded wall of the vessel

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is probably the principal factor in the related vascular spasm. Sympathectomy eliminates the vasoconstriction proximal to the occluded vessel and permits maximal dilation of the collateral vessels. In extensive or far advanced arteriosclerosis the openings to the collateral vessels may also be occluded. In such an instance no beneficial effect will result from sympathectomy.

The sympathetic system controls blood flow through the skin and secretion of the sweat glands. In sympathectomy increased skin circulation and removal of hyperhidrosis are valuable adjuncts in treating superficial ulceration and chronic mild infections of the lower extremities.

Indications

Arteriosclerosis obliterans is the most common cause of ischemia of the lower extremities. The clinical picture, which includes intermittent claudication, coldness, color changes, ischemic pain, ulceration and gangrene, is well known. Although arteriosclerosis is a systemic disease, there has been increased appreciation that one segment of the arterial tree may be affected more than the remainder. The explanation for this segmental involvement is that a thrombus may form on an atheromatous plaque, causing complete occlusion of the vessel. When such occlusion occurs in the distal aorta, or iliac or femoral arteries, the recently developed direct attacks on occlusion by endarteriectomy, resection or bypass graft will give the best long term results for the patient. Aortography and arteriography, in addition to demonstrating the area of occlusion, give the necessary information about the patency of the distal portion of the vessel. When the arteriogram shows a block with little or no distal filling or a patent artery with a markedly narrowed lumen and an irregular outline, direct surgical attack has little to offer the patient. It is in such cases, in which the arteriosclerosis is more generalized, that sympathectomy, by its effect on improving the collateral circulation, has its greatest usefulness. This procedure is also sometimes beneficially combined with the direct approach, particularly to reduce or eliminate arterial spasm in the postoperative period.

Thromboangiitis obliterans or Buerger's disease is an inflammatory disorder of unknown etiology affecting medium-sized arteries, veins and adjacent nerves. Tobacco, as well as other factors, seems to play a role in the disease. The symptoms, resulting from the occluded arteries, are pain, color changes and ulceration. Sympathectomy is helpful in improving the symptoms by increasing the collateral circulation.

Angiospastic disease results from an abnormal vasoconstrictor sensitivity to cold or an emotional disturbance. The characteristic color changes of the skin described by Raynaud in 1862 are typical of the lesions. The skin changes are explained by degrees of vasoconstriction. The white color results from the ischemia due to arteriolar and capillary spasm. With anoxia, the capillary wall relaxes, allowing dilation and retrograde venous dilation and the blue coloration of the skin. The rubor follows relaxation of the arteriolar wall and flushing of the system with oxygenated blood. It would seem that removal of the controlling sympathetic system would relieve all symptoms. However, there is apparently also a local vascular sensitivity in many subjects with angiospastic disease. Sympathectomy may, therefore, produce complete or partial relief of symptoms.

Lumbar sympathectomy has been utilized as an adjunct in the treatment of many other pathologic conditions of the lower extremities. In the occasional case in which vascular spasm is of a severe degree, it may be of real value. In general, however, each case must be individually evaluated with the appropriate tests.

Selection of Patients

It would be ideal if lumbar sympathectomy would provide partial or complete relief of symptoms of all patients with ischemic changes in the lower extremities. However, experience has shown that the procedure is not such a panacea. Unfortunately, there is no reliable method of determining accurately which patient will get a good result from sympathectomy.

All evaluation is made on the basis of a block of the sympathetic nerves with a local anesthetic agent. The improvement in circulation is then measured objectively by oscillometric, plethysmographic or thermometric studies, or subjectively by a trial of ambulation for evidence of relief of symptoms.

The recent introduction of the sympathogalvanic reflex by Lewis has added a refinement which is helpful in evaluating the effectiveness of the sympathetic block. This simple test, using an electrocardiograph to record sympathetic impulses in the extremities before and after sympathetic block, indicates definitely whether or not an effective block has been obtained.

Such information is particularly helpful in borderline cases.

Value of Diagnostic Block: When there is a definite response to sympathetic block, the percentage of patients demonstrating improvement following surgical sympathectomy is high.

In sympathectomy, particularly for arteriosclerotic peripheral vascular disease, the improvement in circulation is due to a more effective collateral circulation. It has been frequently observed that the results from surgical sympathectomy are better than indicated by the diagnostic block. Also, the beneficial effect of sympathectomy is progressive over a period of several weeks. Since a diagnostic block with most anesthetic agents lasts only two to three hours, this may not be of sufficient time to permit more than token improvement in collateral circulation. A phenol sympathetic block, which persists for several months, seems to be a more rational approach to evaluating those patients in which the diagnostic block produced questionable results but who appear clinically to be good candidates for sympathectomy.

Clinical Evaluation: The clinical evaluation of the patient with peripheral vascular disease is of prime importance in determining whether or not he will respond to lumbar sympathectomy. In general, the more severe and generalized the pathologic process, the less the chance of improvement. When death of tissue has already occurred, dilation of collateral vessels will not bring about revitalization of the part. It is possible, however, that sympathectomy in the presence of gangrene may permit amputation at a lower level.

Marked atrophy of the soft parts of the leg, with capillary anoxia and severe pain involving the foot or lower third of the leg, and absent popliteal pulses have been the most constant findings in which minimal effect from sympathectomy has been found.

Results in Peripheral Arteriosclerotic Disease

One hundred patients with arteriosclerotic peripheral vascular disease treated by lumbar sympathectomy at the University of Michigan Hospital from 1953 to 1956 have now been followed up for a period of at least two years. In this group, thirty-eight had bilateral operations, making a total of 138 sympathectomies in the series.

Age and Sex: Eighty-nine of the 100 patients in the group were over fifty years of age (Table I). Of the eleven under fifty years of age, all had confirmatory evidence of degenerative vascular disease by direct examination or by vascular roentgenograms. There were eighty-one men and nineteen women.

TABLE I
Age of 100 Patients Subjected to Lumbar Sympathectomy

Age (yr.)	No.
Under 50	11
50 to 60	38
60 to 70	49
70 or over	2

Preoperative Symptoms and Signs: Most of the patients undergoing sympathectomy had more than one type of symptom (Table II). Intermittent claudication was present in the highest percentage of cases (81 per cent), being the first and most constant symptom in the majority of patients. In most of the patients it appeared after walking one to two blocks. It was present in 115 extremities which were subsequently sympathectomized.

Color Changes and Cold Feet: Fifty-one patients (sixty-nine extremities) noted that they were aware of cold feet. Hyperhidrosis and blanching of the skin of the feet were present in thirty-eight.

Rest Pain: Pain in the foot or toes at complete rest and particularly at night was present in nineteen patients (thirty-one extremities). While this is a common symptom of arteriosclerotic peripheral vascular disease, the low incidence in the present series reflects the selection of the patients. Severe ischemic pain is an indication of severe disease, and in general the results with sympathectomy are poor in patients experiencing this symptom.

TABLE II
Symptoms and Signs in 100 Patients Prior to Lumbar Sympathectomy

Symptom	No. of Extremities	No. of Patients
Intermittent claudication	115	81
"Cold feet"	69	51
Rest pain	31	19
Tissue necrosis	34	16
Absent dorsalis pedis	124	90
Absent popliteal pulse	94	68

TABLE III
Amputations Following Lumbar Sympathectomy

Duration	No. of Extremities	No. of Patients
Within one year	28	20
After one year	11	8
Total	39	28

Ulceration: Tissue necrosis was present in sixteen patients (thirty-four extremities). In general, this was confined to superficial ulceration below the ankle and in a few patients included some gangrene of portions of the toes.

Pulses: The dorsal pedis pulse was absent in 124 (90 per cent) of the extremities in which sympathectomy was carried out. The popliteal pulsation was also absent in ninety-four (68 per cent) of the extremities.

Sympathetic Block: In eighty-six patients sympathetic block was carried out as a preoperative diagnostic test. In forty-three cases (fifty-eight extremities) there was evidence of a rise in skin temperature of 3°F. or more or a good subjective response. In twenty-eight cases (thirty-nine extremities) the testing showed some improvement. In fifteen cases (twenty-one extremities) there was minimal or no response.

Diabetes: Diabetes mellitus was present in thirty-one patients in this series. The diagnosis of this disorder was established during the work-up for the peripheral vascular disease in eleven patients.

RESULTS

Death: Two deaths occurred in the immediate period of hospitalization: one on the third and the other on the seventh postoperative day. Both were the result of coronary artery occlusion, as demonstrated at autopsy. In the period of follow-up, thirteen other patients have died. Of this group, nine deaths were attributed to complications of arteriosclerosis, two to unrelated causes, and in two the cause of death was not known.

Amputation: Major amputations were performed on thirty-nine extremities (28 per cent) in which sympathectomy had been performed (Table III). It is noteworthy, however, that twenty-eight (20 per cent) were performed in the first year postoperatively. In the patients who had late amputation, there was a period of months in which the preoperative symptoms were partially or completely relieved. Amputations were twice as common in patients with diabetes than in those without diabetes.

Symptomatic Improvement: The interval from the time of operation is a factor in determining how much relief or improvement of symptoms had been obtained. Many patients had relief of symptoms initially but later the symptoms returned. The length of time the patient had relief was dependent on the progression of the arteriosclerotic obliterative disease.

In this series intermittent claudication was significantly relieved in 51 per cent of the patients. Two-thirds of the patients reported their feet were warmer after sympathectomy. Rest pain was relieved in one-third of the patients. Ulceration, with or without amputation of digits, was improved or healed in 60 per cent of the extremities after sympathectomy.

CLASSIFICATION OF RESULTS

In 100 patients, 138 lumbar sympathectomies were carried out. Results were evaluated at least two years after operation (Table IV).

TABLE IV
Classification of Results Following Lumbar Sympathectomy

Result	No. of Extremities	No. of Patients
Good	70	52
Fair	23	17
Poor	45	31
Total	138	100

Good Results: Patients were considered to have a good result if for a period of at least one year they had significant or complete relief of preoperative symptoms. Fifty-two patients fell into this group. Patients who later underwent amputation are included but only if symptoms returned or became worse after one year.

Fair Results: Patients were considered to have a fair result if they had partial improvement or relief of symptoms and no amputation during the first postoperative year. This group was comprised of seventeen patients.

Poor Results: Patients without relief of symptoms and those undergoing major amputation in the first year postoperatively were included in this group (thirty-one patients).

Summary

Lumbar sympathectomy is a valuable palliative procedure in the treatment of selected cases of peripheral vascular disease. Clinical evaluation, plus objective and subjective response to lumbar sympathetic block, is helpful in selecting patients who will probably be helped by lumbar sympathectomy. Patients may have improvement of symptoms following lumbar sympathectomy but recurrence may occur later as the arteriosclerotic disease progresses. The results in a series of 138 sympathectomies in 100 patients are reported.

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Symposium on Phonocardiography

Ultra Low Frequency Precordial Movements—Kinetocardiograms*

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Kinetocardiograms are the graphic representation of ultra low frequency displacement precordial vibrations. The frequency components of these motions usually lie between 1 and 10 cycles per second; however, Fourier analysis has revealed higher frequencies present but of less significance. As the energy of low frequency movements is proportionately greater than that of the high frequencies, the relative amplitude of the higher components is less, making it unnecessary to use band pass filters. This eliminates the problem of phase shift and amplitude distortion of the trace as a result of the amplifier or electronic equipment.

Method of Recording

The apparatus for recording kinetocardiograms consists of a flexible metal bellows which is responsive to low frequencies. The bellows has a probe on one side which is approximately 7 mm. in diameter and can be placed wherever desired. The open end of the bellows is connected by a short piece of rubber tubing to a pressure transducer (Statham P5A). The output is fed into a carrier amplifier and can be registered by any number of recording devices, including the Sanborn Polyviso or the Scheiner Electronic Recorder. The bellows is mounted from a crossbar suspended above the patient so that absolute motions of the chest wall can be obtained. In order to insure that motions of the precordium are registered linearly and without phase shift, it is desirable to mount the bellows from a fixed point above the chest wall and to record the motion of a single point. This is considered important for several reasons. Any device which rests directly upon the chest yields records which are the result of the differential motion of the rim and the sensing point (probe or diaphragm). Therefore, some phase shift occurs in the trace which is unpredictable, depending upon the character of the relative motion. Even though one uses displacement pickup devices, some of the frequency components may actually be velocity rather than displacement as a result of this differential motion. In addition, amplitude changes occur which are the result of the phase shift. The degree of phase shift as the result of the relative motion is dependent at least in part upon the size of the rim of the pickup device. For example, if one records the apex cardiogram with various funnels of different diameters, the registered trace will vary considerably both in configuration as well as in temporal relations. In addition, motions of the entire chest wall will be minimized or poorly registered by such a device. Therefore, tracings will vary from one laboratory to another unless some uniform standardization of the pickup device which rests upon the chest wall is achieved. In contrast, any displacement pickup device mounted above the chest wall gives records which are linear, do not have the phase shift distortion, and can register displacement movements of the precordium which will be comparable from any laboratory.

Numerous pickup devices have been tested and any linear displacement device, if mounted in this fashion, gives tracings which are identical. The bellows was selected only because of its

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simplicity and accuracy. One disadvantage is that records have to be obtained during held respiration. Consideration has been given as to whether or not the pressure of the bellows against the chest wall in itself alters the motions recorded. However, other pickup devices using less pressure give the same records, and even photocell tracings in which there is no coupling of the chest wall to the photocell yields the same traces as obtained with the bellows. It is pointed out that these objections to transducers which rest upon the chest wall do not necessarily mean that such technics may not be clinically useful or important; however, the kinetocardiographic technic does facilitate easy standardization, reproducibility, and its clinical value and reliability are in the process of being delineated.

Traces are usually taken from many points over the precordium and epigastric areas, usually corresponding to the V leads of the electrocardiogram and labeled K_1, K_2, etc. Epigastric traces are taken from the subcostal margins in the right and left mid-clavicular lines, in the mid-epigastric area and labeled KER, KEL and KEM, respectively. Further technical discussions of the problems in recording precordial chest wall motions have been reported elsewhere.[1–3]

Applications

The understanding of the kinetocardiograms is best approached from the standpoint that the vibrations recorded in the ultra low frequency displacement traces are simply those which often can be seen and felt at the bedside. An example of this is the apex thrust in left ventricular hypertrophy or the parasternal lift which is associated with right ventricular hypertrophy. The traces, therefore, represent an accurate graph of these movements.

The previous work with this technic has been published elsewhere and includes studies of the normal patterns,[1] normal variation,[4] and in addition a number of clinical studies which are primarily descriptive as to the types of patterns noted in various types of heart disease. These include studies of valvular heart disease,[5–7] the pre- and postoperative changes as a result of mitral commissurotomy,[8] and the registration of myocardial paradoxic bulges in patients with myocardial infarction[9] as well as in angina pectoris.[10]

Rather than review the previously published reports, as done elsewhere[3] the following two papers will present some recent investigations with this technic that illustrate its potential clinical usefulness. The first paper correlates the kinetocardiogram with the electrocardiogram, fluoroscopic examination and right heart catheterization findings in a group of patients with heart diseases that lead to right ventricular hypertrophy. In addition, it points out means by which right ventricular pressure loads can be separated by the use of the kinetocardiographic traces from right ventricular flow loads. The second paper presents the first attempt to correlate measurements from the kinetocardiographic traces quantitatively with the pulmonary artery pressure and total pulmonary vascular resistance. Although it is obvious from the data that there are instances in which the tracings apparently do not reflect accurately the pulmonary artery pressure, a significant correlation is established. Even with these limitations, we consider this paper particularly important, as it demonstrates that the kinetocardiogram does show a definite relationship to other more precise physiologic measurements and possibly opens the door to further quantitation of the traces. It is hoped that with either this or some new type of analysis it may be possible to approach the kinetocardiographic traces quantitatively and rationally, rather than empirically.

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The Recognition and Differentiation of Right Ventricular Pressure and Flow Loads

A Correlative Study of Kinetocardiograms, Electrocardiograms, Fluoroscopy, and Cardiac Catheterization Data in Patients with Mitral Stenosis, Septal Defect, Pulmonic Stenosis and Isolated Pulmonary Hypertension*

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Many clinicians have relied considerably on precordial palpation for the diagnosis of right ventricular hypertrophy or over-function; however, this has never been fully documented and the value of palpation in relationship to other diagnostic methods has not been established. The present study undertakes to delineate the value of records of precordial motion (kinetocardiograms) in the diagnosis of right ventricular predominance and to correlate the findings with cardiac catheterization data, electrographic findings and fluoroscopic observations in patients with mitral stenosis, atrial septal defect, pulmonic stenosis and isolated pulmonary hypertension. The present study also offers some clues as to the genesis of the kinetocardiograms (precordial movements)in patients with right ventricular hypertrophy.

Methods

The only basis for the selection of patients in this study was the availability of kinetocardiograms, right-sided cardiac catheterization data, fluoroscopic examinations and electrocardiograms. Included are twenty patients with mitral stenosis, eleven with atrial septal defects, two with pulmonic stenosis and two with isolated pulmonary hypertension. All but three of the patients with atrial septal defects were presumed to have ostium secundum defects, while in these three patients it was uncertain whether or not the interatrial defect was of the primum or the secundum type. However, as both defects lead to right ventricular hypertrophy, they were included in the series.

Technics: The technic for recording the kinetocardiograms (ultra low frequency precordial movements) and the patterns found in normal subjects have been previously described.[1–3] A bellows was attached to a cross bar mounted above the patient in order to obtain absolute movements of the chest wall. The bellows was connected to a low pressure Statham strain gauge or piezoelectric transducer by a short segment of rubber tubing. Simultaneous electrocardiograms and carotid pulses were obtained as timing references. Traces obtained by this technic represent the absolute movements of the precordium and not relative interspace motion and therefore can be considered to be the graphic representation of the movements palpated at the bedside. The fluoroscopic examinations were made by several different physicians; however, all were considered competent cardiac fluoroscopists. Right heart catheterization was performed in the usual manner; pressures were determined by use of a Statham P23A or D strain gauge. The mean value for pulmonary artery pressure was determined electrically. A Sanborn Polyviso was employed for recording the kinetocardiograms and an oscilloscope multichannel instrument† for determining cardiac catheterization pressure data.

Electrocardiographic Criteria: As there is no uniform agreement as to which electrocardiographic changes represent right ventricular hypertrophy, the findings are listed arbitrarily according to the various pat-

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terns. An "rsr' " in lead V_1 without QRS prolongation is termed incomplete right bundle branch block. A qR complex in lead V_1 with intrinsicoid prolongation and without marked prolongation of the total complex is termed right ventricular hypertrophy. A qR complex in lead V_1, a markedly slurred S in lead I and total QRS duration of 0.12 second or longer is classified as right bundle branch block. Only when the electrocardiogram is unequivocally within normal limits is it listed as normal.

Kinetocardiographic Analysis: Measurements utilized in this study were made from the kinetocardiographic trace recorded from the lead V_2 precordial electrocardiographic position and labeled K_2. The duration of the initial outward systolic movement (beginning between 0.03 and 0.07 second after the QRS onset) was measured as subsequently described. The ratio herein presented was obtained by dividing the amplitude of the early initial systolic outward movement by the pull-in or retraction during early ejection. Normal standards were obtained from a group of forty-four normal subjects. Certain variations of the early systolic outward portion of the normal kinetocardiogram present some difficulty in measurement, as illustrated in Figure 1; however, in the records from patients in the present study the onset of the movement offers no problem since it is exaggerated in amplitude. In both normal and abnormal records the onset of the early outward movement as stated usually begins between 0.03 and 0.07 second after the onset of the QRS complex. This outward movement is absent in 30 per cent of the normal subjects, assuming that it begins within the time limits presented. The movements in the traces of auricular origin (those which begin after the P wave and before the onset of the QRS complex) extend to the initial portion of the trace and may fuse with the ventricular movements (Fig. 1). A sharp break in the trace usually occurs with the onset of right ventricular activity which marks the separation of the outward movement from those of auricular origin. The onset of the ventricular movement then is considered the point from which the horizontal baseline is drawn. From this amplitude of the initial outward movement is determined. The retraction is the amplitude from the peak of the outward movement to the point of greatest retraction in early systole. This is illustrated in Figure 1 and examples of the normal variations are presented. Using the same baseline, the duration is the time from the onset of the outward movement to the point where the trace subsequently crosses the baseline (Fig. 1).

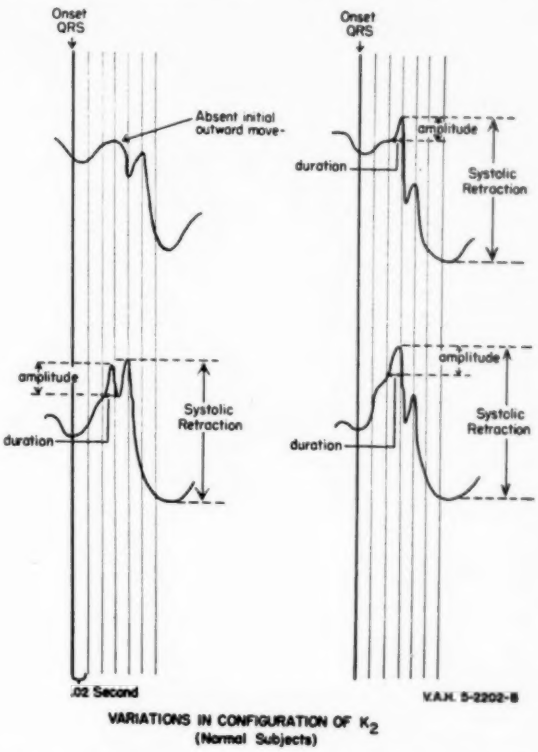

FIG. 1. Drawings representing the variations in the normal kinetocardiogram from the lead V_2 position. Approximately 30 per cent of the normal subjects have an absence of the initial outward movement beginning between 0.03 and 0.05 second after the onset of the QRS complex as illustrated in the upper left hand figure. Note in the other drawings the movements due to auricular activity extend into the initial portion of systole; however, these are easily separated from the ventricular portion of the trace by abrupt slope change in the trace. This is the point selected for the horizontal line measurements of amplitude as well as duration of the movement.

RESULTS

The typical configuration of the kinetocardiograms in patients with mitral stenosis has been previously described in detail[4,5] and consists chiefly of an abrupt outward movement of the precordium beginning approximately 0.03 to 0.07 second after the onset of the electrocardiographic QRS complex (Fig. 2). This outward motion is interrupted by a small inward motion at the time of left ventricular ejection (determined by the upstroke in the carotid pulse); however, this is terminated very quickly by a continuing outward motion of the precordium reaching a peak usually in mid-systole. Thus the entire precordium has a rather sustained outward movement throughout systole. This motion is easily palpable or can be observed visually at the bedside in almost all patients with mitral stenosis.

This precordial heave or outward motion of the precordium may be most marked either to the right of the sternum or to the left of the sternum. In a previous communication[4] these were divided into various types depending upon the di-

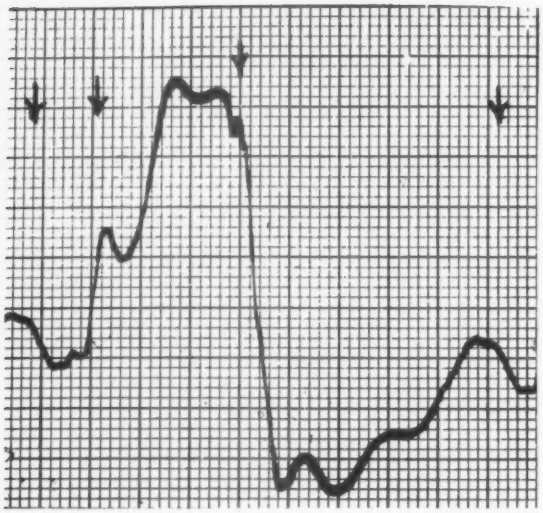

FIG. 2. Kinetocardiogram of a patient with mitral stenosis taken from the lead V_2 point. A paper speed of 50 mm. per second was used for all records. The first arrow indicates the onset of the QRS complex of the electrocardiogram, the second arrow the upstroke in the carotid pulse, the third arrow the carotid incisural notch and the fourth arrow the onset of the succeeding QRS complex. There is a prominent outward movement beginning before the ejection as determined by the upstroke in the carotid pulse, and shortly after the onset of ejection (second arrow) there is a brief retraction followed by a marked mid-systolic outward movement. The mid-systolic outward movement is most prominent in patients with severe pulmonary hypertension. The amplitude of the initial outward movement just before the upstroke in the carotid pulse (second arrow) divided by the amplitude of the pull in during the early part of ejection (the brief inward movement after the second arrow) in this instance gives a ratio of 4. Note that the total outward movement of the precordium is quite broad, having a duration of 0.34 second, taking the baseline as the onset of the point where the initial upward movement begins.

rection of the precordial heave. The records in which the motion was most marked to the right of the sternum with an inward motion occasionally at K_3 and always at K_4 were classified as type I while those directly (extending from K_2 to K_4) to the left of the sternum with a normal outward movement at K_1 were classified as type II records. Thus K_2 was most consistently abnormal. Type III records were those showing a double outward early systolic movement instead of a single outward movement; however, it has become apparent from further observations that type III records probably represent only a minor variant of type II and the difference is probably of no significance. In this study type III records are classified as type II traces.

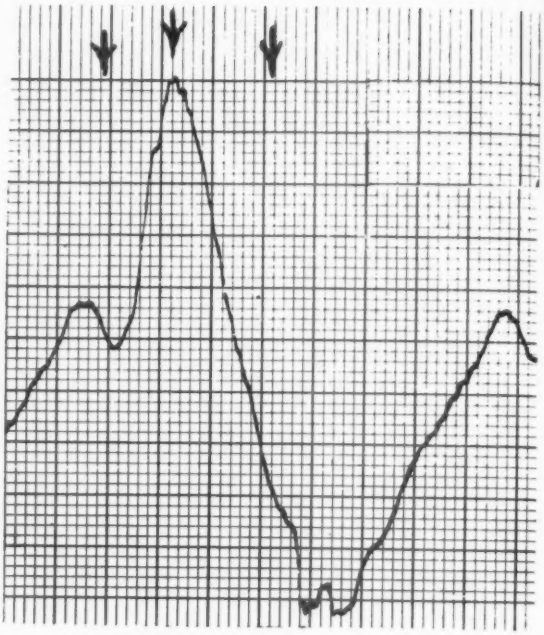

FIG. 3. Precordial trace from a patient with atrial septal defect without significant pulmonary artery hypertension. The first arrow indicates the onset of the QRS complex in the electrocardiogram, the second arrow the onset of ejection as determined by the upstroke in the carotid pulse and the third arrow the carotid incisural notch. Note the prominent early systolic outward movement which reaches a peak at the onset of ejection (second arrow), followed by a prominent inward movement of the precordium. In this instance there is no mid-systolic outward movement noted. The ratio in this instance would be the expression of the amplitude of the initial systolic outward movement to the amplitude of the inward motion which occurs during the period of ejection. In this instance the ratio is approximately 0.5, well below that noted in patients with mitral stenosis who have elevation of the pulmonary artery pressure. In addition the outward movement is rather brief in duration. Taking the point of onset of the outward movement as the baseline and measuring across in seconds the duration of the outward movement is only 0.22 second in contrast to patients with pulmonary hypertension who all have a duration of over 0.3 second in every instance.

Table I lists the data from the twenty patients with mitral stenosis. Note that all patients had the typical kinetocardiographic findings as described, while the pulmonary artery pressures varied from as high as 138/70 to a low mean of 20 mm. Hg. Ten of the twenty patients had electrocardiograms which had to be considered as normal. None of these classified as normal had the R wave of greater amplitude than the S wave in lead V_1. In addition, the mean QRS axis in the group considered as normal was never greater than 90 degrees. Thus 50 per cent of the twenty

patients had normal electrocardiograms. Fluoroscopic examination revealed that eight of the twenty patients (40 per cent) had no detectable right ventricular enlargement.

The ratio obtained by dividing the amplitude of the early initial outward systolic movement of the kinetocardiographic traces by the pull-in or retraction during early ejection is listed in Table I. Measurements were made from the K_2 position. Note that all patients with mitral stenosis had a ratio of 1 or greater. The ratio for normal subjects ranges from 0 to 0.40, with a mean of 0.104 and a standard deviation of 0.167. In other words, in the patients with mitral stenosis the retraction of the precordium during the initial phase of the ejection was never greater than the amplitude of the early outward movement. In addition, if one measures the breadth in seconds of the outward movement, taking the point of the onset as the baseline, the duration ranged from 0.30 to 0.40 second. The duration in normal subjects has a range of 0.01 to 0.05 second, a mean of 0.029 second with a standard deviation of 0.013 second.

ATRIAL SEPTAL DEFECT

There were eleven patients in the series with atrial septal defect, four of whom had significant pulmonary hypertension (Cases 1, 2, 3 and 4) (Table II). Kinetocardiograms from the patients with normal or minimally elevated pulmonary artery pressure were characterized by a marked early systolic outward movement comparable in time and configuration to the early outward movements noted in patients with mitral stenosis. However, in contrast to the findings in patients with mitral stenosis there was a marked retraction of the precordium beginning about the onset of ventricular ejection and lasting throughout systole. Figure 3 illustrates a typical trace from a patient with an atrial septal defect without significant elevation of the pulmonary artery pressure. The ratio obtained by dividing the amplitude of the initial outward movement by the retraction was less than 1 in all of these patients with relatively normal pulmonary artery pressures. Three of the patients had ratios within the normal range. However, all patients had significant differences in the dur-

TABLE I
Findings in Patients with Mitral Stenosis

Case No.	Mean Pulmonary Artery Pressure (mm. Hg)	Fluoroscopy, Enlargement of Right Ventricle	Electrocardiogram	Mid-systolic Outward Movement	Ratio	Duration of Outward Movement (sec.)	Type
1	PA = 138/70	Moderate	RVH	Marked	23	0.30	I
2	95	No	Normal	Marked	5	0.39	I
3	77	Moderate	RVH	Marked	23	0.38	I
4	PA = 121/64	No	RVH	Marked	1.8	0.38	I
5	PA = 100/50	Moderate	Right axis only	Marked	14.5	0.38	I
6	67	No	Normal	Marked	4	0.34	I
7	52	Moderate	RVH	Marked	10	0.40	I or II
8	70 (systolic)	No	RVH	Marked	1.6	0.34	I
9	48	Minimal	Normal	Marked	1.76	0.40	I
10	37	Moderate	ICRBBB	Marked	30	0.40	II
11	35	No	Normal	Marked	1	0.34	II
12	35	No	RVH	Marked	2.7	0.40	II
13	RV = 54/0	Minimal	Normal	Marked	2.42	0.42	II
14	PA = 55/21	Moderate	Normal	Moderate	10	0.40	II
15	33	Minimal	ICRBBB	Marked	8.3	0.36	II
16	PA = 48/18	Moderate	Normal	Marked	1	0.38	II
17	29	Minimal	ICRBBB	Marked	2.8	0.37	II
18	26	Moderate	Normal	Marked	1.8	0.38	II
19	25	No	Normal	Minimal	1	0.40	II
20	20	No	Normal	Marked	10	0.40	II

NOTE: PA = pulmonary artery systolic and diastolic pressure. RV = right ventricular pressure. RVH = right ventricular hypertrophy. ICRBBB = incomplete right bundle branch block. Ratio = amplitude of initial early systolic movement divided by systolic retraction.

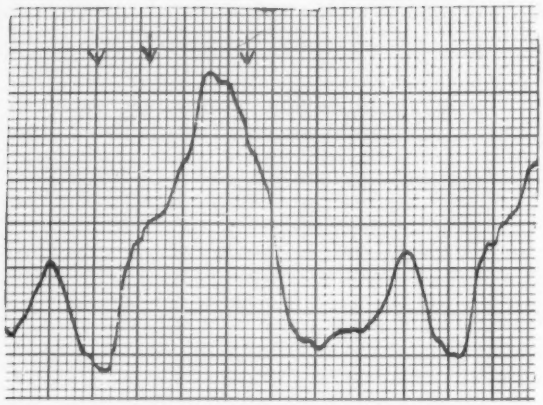

FIG. 4. Kinetocardiographic trace from the lead V_2 point from a patient with atrial septal defect and elevation of the pulmonary artery pressure. The first arrow indicates the onset of the QRS complex in the electrocardiogram, the second arrow the onset of ejection as determined by the upstroke in the carotid pulse and the third arrow the carotid incisural notch. Again note the prominent early outward movement of the precordium which begins approximately 0.04 second after the onset of the QRS complex. There is no retraction of the precordium during the early ejection period but a continuing outward movement reaching a peak in mid-systole. Note that the total breadth of the complex is markedly increased similar to that noted in patients with mitral stenosis and pulmonary artery hypertension.

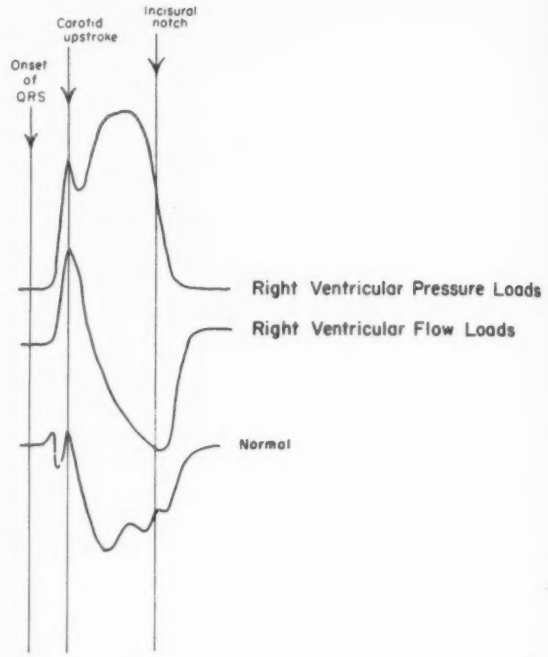

FIG. 5. Schematic drawing demonstrating the differences in the kinetocardiograms from patients with right ventricular pressure loads and right ventricular flow loads and normal subjects. Note that the patients with pressure loads show a marked mid-systolic outward movement in contrast to the retraction of the precordium in patients without significant pulmonary artery pressure elevation and with increased flow loads. Also note that the ratio of the initial outward movement to the retraction during ejection in patients with right ventricular hypertrophy and elevated pulmonary artery pressures would be greater than 1. The total duration of the over-all outward movement would be considerably prolonged in patients with right ventricular pressure loads. The ratio of the initial outward movement to the retraction would be considerably less than 1 in patients without pulmonary hypertension and the duration of the outward precordial movement would be considerably less than that noted in patients with pulmonary artery hypertension. The differences from normal are obvious.

ation of the movement. In other words, the retraction during ejection of the precordium was aways greater than the initial outward movement in patients with atrial septal defects without significant pulmonary artery hypertension. In addition, the duration of the movement was always less than 0.26 second in contrast to the much longer duration noted in patients with mitral stenosis (0.30 to 0.42 second). The duration of the outward movement was also significantly prolonged when compared to the values found in normal subjects (over twice the standard deviation from the normal mean of 0.029 second).

The four patients in whom the pulmonary artery pressure was markedly elevated revealed in addition to the early prominent outward systolic motion a mid-systolic outward movement similar in pattern to the traces from patients with mitral stenosis (Fig. 4). These patients also had ratios which were elevated. Furthermore the duration of the outward movement was considerably prolonged (0.30 to 0.46 second), again similar to the data from the patients with mitral stenosis and elevated pulmonary artery pressures (Table II).

All patients with atrial septal defects had abnormal electrocardiograms, characterized chiefly by a right bundle branch block, incomplete right bundle branch block or right ventricular hypertrophy. Fluoroscopic examination revealed only one patient with no detectable right ventricular enlargement.

PULMONIC STENOSIS

Only two patients with pulmonic stenosis were studied and both of these had kinetocardiographic traces similar in configuration to the traces from patients with mitral stenosis (Table II). One of these patients had a normal electrocardiogram and only minimal enlargement of the right ventricle on fluoroscopic examination. The ratio of

TABLE II

Findings in Patients with Congenital Lesions Associated with Right Ventricular Dysfunction

Case No.	Cardiac Catheterization Findings			Fluoroscopy, Enlargement of Right Ventricle	Electrocardiogram	Kinetocardiographic Findings			
	Mean Pulmonary Artery Pressure (mm. Hg)	Right-Left Shunt Flow (L./min.)	Left-Right Shunt Flow (L./min.)			Early Systolic Outward Movement	Mid-systolic Outward Movement	Ratio	Duration of Outward Movement (sec.)
Patients with Atrial Septal Defect									
1	RV = 75/0	...	...	Moderate	RVH	...	Marked	3.0	0.42
2	78	1.8	0.36	Moderate	RVH	...	Marked	1.5	0.36
3	40	0.7	1.8	Marked	RBBB	...	Marked	∞	0.46
4	32	4.5	9.0	Marked	RBBB	...	Marked	24.0	0.38
5	22	...	14.0	No	RVH	Marked	None	0.20	0.16
6	20	...	7.8	Moderate	ICRBBB	Marked	None	0.33	0.08
7	19	...	4.8	Moderate	RVH	Moderate	None	0.24	0.09
8	19	...	9.15	Minimal	RVH	Moderate	None	0.94	0.26
9	18	...	2.4	Moderate	Left axis	Moderate	None	0.42	0.22
10	18	...	15.6	Minimal	RBBB	Marked	None	0.77	0.20
11	8	...	18.7	Moderate	ICRBBB	Marked	None	0.55	0.17
Patients with Pulmonic Stenosis									
12	RV = 146/21	...	...	Marked	RVH	...	Moderate	1.2	0.34
13	RV = 56/3	...	...	Minimal	Normal	Moderate	Marked	3	0.40
Patients with Isolated Pulmonary Hypertension									
14	53	...	...	Moderate	RVH	...	Marked	100	0.38
15	PA = 84/52	...	...	Moderate	RVH	...	Marked	5	0.30

NOTE: Abbreviations are the same as for Table I.

the initial outward movement to the systolic retraction was greater than 1 in both of these patients and in both the duration was also prolonged.

ISOLATED PULMONARY HYPERTENSION

The two patients with isolated pulmonary hypertension had tracings similar in type to patients with mitral stenosis. Both had electrocardiograms compatible with right ventricular hypertrophy and moderate enlargement of the right ventricle was observed on fluoroscopic examination. The ratio and duration of the precordial outward movement was within the range present for the patients with mitral stenosis.

COMMENTS

Clinical evaluation of right ventricular function or size has been approached in several ways. Enlargement can be estimated from fluoroscopic examination but this does not distinguish between hypertrophy and dilatation. The electrocardiogram gives some index to hypertrophy; however, hypertrophy can be present with a normal electrocardiogram.[5,6] In addition, there is still confusion as to which changes in the electrocardiogram are due to hypertrophy and which are due to ventricular dilatation. Also, any changes noted will not reflect the functional status of the myocardium. The information as obtained by these technics (fluoroscopy and electrocardiography), although useful, appears limited. The electrocardiogram was entirely normal in 29 of the patients in the present series and, if one considers the group with mitral stenosis alone, 50 per cent were normal. Enlargement of the right ventricle was noted by fluoroscopy in only 74 per cent of the patients and in

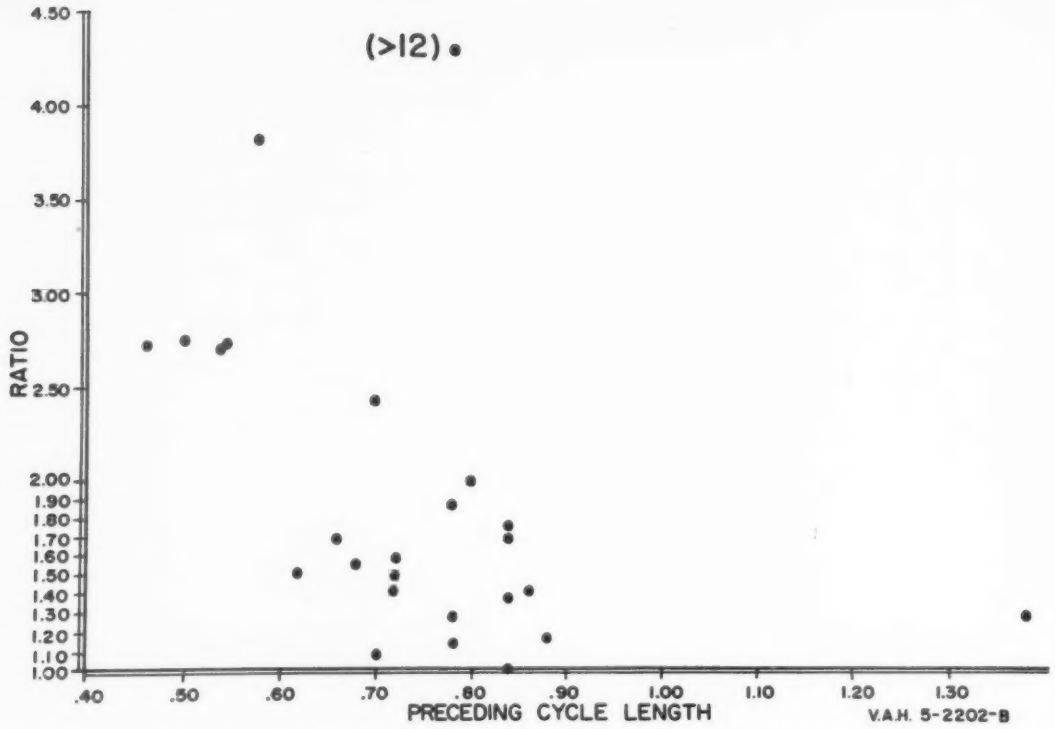

FIG. 6. Correlation of the ratio, as obtained by dividing the amplitude of the initial outward systolic movement by the amplitude of retraction during systole, to the preceding cycle length in a patient with mitral stenosis and auricular fibrillation (Case 19, Table I). Note that the ratios tend to be small when the preceding cycle length is long and vice versa. This points to the fact that the inward movement during ejection is related at least in part to stroke volume. Therefore the ratio is reduced when the stroke volume is large. However, the duration of the outward movement did not change.

60 per cent of the group with mitral stenosis.

Right Ventricular Pressure Load vs. Flow Load: The kinetocardiogram was abnormal in all patients studied due to the prolongation of the initial outward systolic movement (0.08 to 0.46 second, the normal being 0.029 second with a standard deviation of 0.013 second). Thus, the kinetocardiogram reflects in some way the abnormal situations placed upon the right ventricle. Not only were the precordial movements abnormal in all patients studied, but pressure loads are also reflected differently from the flow loads. Both defects produce a prominent initial outward systolic movement (Figs. 1 and 3), whereas retraction during systole takes place in patients with flow loads in contrast to those with pressure loads in whom there is a prominent mid-systolic outward movement. These are easily separated not only by inspection but also by the ratio of the duration of the movement (Tables I and II). The fact that the patients with only flow loads on the right ventricle had ratios less than 1, whereas all patients with elevated pulmonary artery pressure had ratios greater than 1, including the four patients with atrial septal defect and reversed shunt, appears significant. In addition, the duration of the outward precordial heave was considerably lengthened in patients with pressure loading in contrast to the briefer outward movement in patients with lower pulmonary artery pressures. In all groups as stated, the traces were significantly different from that found in normal subjects. Figure 5 illustrates the right ventricular pressure loading as contrasted with right ventricular flow loading, as well as the normal trace.

Kinetocardiogram in Pulmonary Hypertension: It is also apparent that the kinetocardiographic traces may give some indication as to the severity of pulmonary artery pressure elevation. From Table I it is noted that all patients with mitral stenosis and markedly elevated pulmonary artery pressures had the type I trace, or a trace in which the outward movement of the precordium was prominent over the right side of the chest. All those with lower pulmonary artery pressures

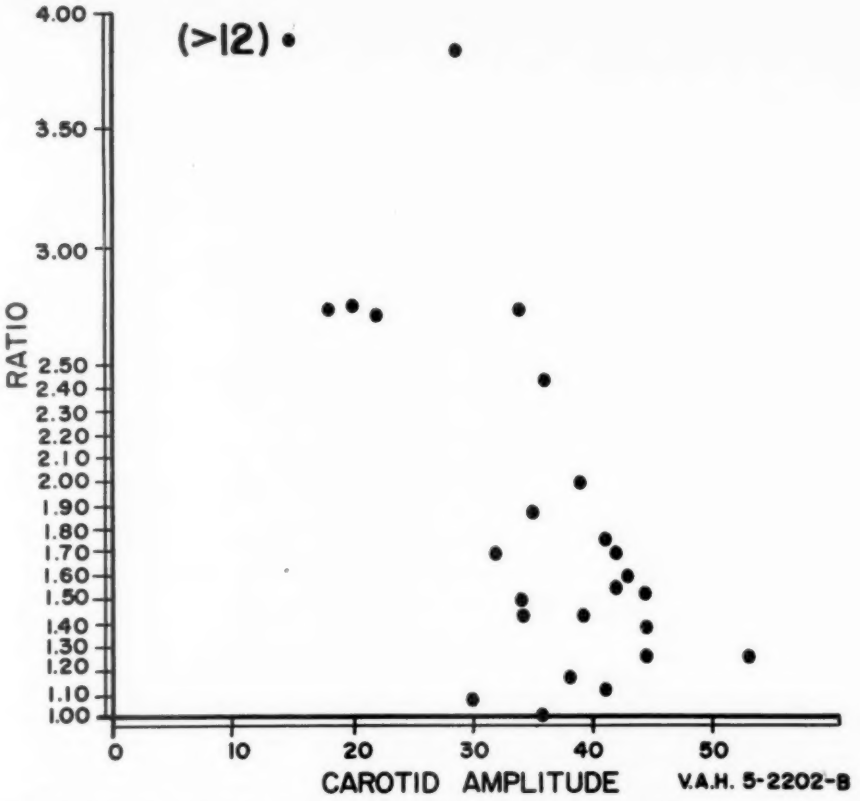

FIG. 7. Correlation of the ratio, as obtained by dividing the amplitude of the initial outward systolic movement by the retraction of the precordium during ejection, with the amplitude of the carotid pulse. Note that the beats with large carotid amplitudes had ratios which tended to be small and vice versa. This again illustrates the influence of stroke volume upon the ratio.

had the precordial outward movements to be most prominent in the left lower parasternal region of the chest. One patient was classified as type I or II since the "heave" was equally prominent over the lower right and left side of the chest. Note that there was not a single patient with a type I trace with a pulmonary artery mean pressure under 37 mm. Hg. Therefore, the kinetocardiogram may not only reflect hypertrophy and pulmonary pressure elevations but also may give some clue as to the degree of pulmonary hypertension.

Ratio of Amplitude of Initial Outward Movement Divided by Systolic Contraction: The ratio as determined by dividing the amplitude of the initial outward movement by the systolic retraction deserves further comment. Obviously the degree of retraction during systole would affect the values considerably and it was expected that the ratio would vary somewhat from beat to beat in patients with auricular fibrillation. Table III lists the ratios as determined from a patient with mitral stenosis (Case 19, Table I). In addition, the duration of the previous cycle length is listed as well as the amplitude of the carotid pulse (the carotid pulse is not quantitated but gives some crude estimation of the stroke volume). Note that the ratio tends to be small when the previous cycle length is long and vice versa (Fig. 6). The ratio is also small when the carotid pulse is large (Fig. 7). These findings indicate that the degree of systolic retraction is related to stroke volume and that when the stroke volume is large the ratio is reduced. In this patient, nevertheless, the duration remained constant. Patients with mitral stenosis, pulmonary hypertension and auricular fibrillation rarely have a ratio below 1; however, if one analyzes several complexes, the values still fall within those presented in this study.

The ratios for the patients with atrial septal defects and without significant pulmonary hyper-

TABLE III

Variations in Carotid Amplitude, Ratio and Preceding Cycle Length in a Patient with Auricular Fibrillation and Mitral Stenosis (Case 19)

Carotid Amplitude (mm.)	Ratio	Preceding Cycle Length (sec.)
44	1.38	0.84
34	2.73	0.54
42	1.56	0.68
44	1.53	0.62
44	1.27	1.38
43	1.60	0.72
36	1.00	0.84
20	2.75	0.50
32	12.00	0.80
30	1.09	0.70
32	1.70	0.66
34	1.42	0.72
22	2.71	0.54
39	2.00	0.80
36	2.43	0.70
18	2.73	0.46
29	3.83	0.58
35	1.89	0.78
53	1.29	0.78
38	1.16	0.88
39	1.43	0.86
42	1.71	0.84
34	1.50	0.72
41	1.75	0.84
41	1.14	0.78

tension are below 1, possibly because of the increased stroke volume, while the four patients with pulmonary hypertension tend to have smaller total flow or stroke volumes. This possibly accounts for some, but not all, of the differences noted, as one patient (Case 4, Table II) with increased pulmonary artery pressure had a total pulmonary flow of 12.9 L. per minute and yet had a ratio of 24, and the outward movement had a duration of 0.38 second. However, it is possible that the ratio and duration of the outward movement may not aid in estimating pulmonary hypertension when there is a marked increase in minute flow but this increased cardiac output is usually obvious clinically. The duration of the outward movement nevertheless still separates the abnormal from the normal traces.

Genesis of Kinetocardiogram: The question of the genesis of the kinetocardiogram arises and only a few ideas can be presented. At present it appears that the movements are in some way related to right ventricular function, as mentioned. The initial systolic outward movement is present in traces from both pressure and flow loads. The only apparent common denominator between the two conditions appears to be the presence of true right ventricular hypertrophy (increased weight of right ventricle). Previous follow-up studies in patients with mitral stenosis appear to support this hypothesis. The exaggeration of this outward movement persisted in these patients following successful commissurotomy for as long as a year[7] and one would suspect that the features in the traces, if due to true hypertrophy, would persist at least for a while. The presence of a mid-systolic outward movement appears to be related to pressure loading of the right ventricle, as well as the possible influence of stroke volume, as previously discussed and illustrated in Figures 6 and 7. In addition, the prominent mid-systolic outward movement often diminished considerably as early as ten days after commissurotomy in patients with mitral stenosis.[7] Similarly in the four patients with atrial septal defect and pulmonary artery hypertension with a reversal of shunt flow the mid-systolic outward movement was prominent. Therefore, it would appear that the pressure loading probably is the most significant factor in determining the mid-systolic outward movement. Thus the initial outward movement is possibly related to true right ventricular hypertrophy while the mid-systolic outward movement is related to pressure loading; however, without right ventricular weight it is impossible to state with certainty whether or not there is right ventricular hypertrophy in the group of patients studied.

Obviously the results of this study apply only to the etiologies as listed; however, it is probably true that the criteria as outlined may apply in general to patients with right ventricular abnormalities due to other causes.[8] Obviously the alterations in the thoracic cage in patients with pulmonary emphysema may distort the location and amplitude of the precordial heave and occasionally the outward movement may be most pronounced in the epigastric areas rather than over the precordium. Whether or not these findings are applicable to all patients with right ventricular dysfunction still remains to be determined.

Summary and Conclusions

1. A correlative study of kinetocardiograms, cardiac catheterization data, electrocardiograms and fluoroscopic examinations was made on a group of twenty patients with mitral stenosis,

eleven patients with atrial septal defect, two patients with pulmonic stenosis and two patients with isolated pulmonary hypertension.

2. Kinetocardiograms were abnormal in all patients studied, whereas the electrocardiogram was within normal limits in 29 per cent of the patients. Fluoroscopy revealed no right ventricular enlargement in 26 per cent of the patients. When the patients with mitral stenosis were considered singularly the kinetocardiograms showed evidence of right ventricular flow or pressure loads in all patients, while 50 per cent of the patients had normal electrocardiograms and 40 per cent had no enlargement of the right ventricle on fluoroscopy.

3. Patients with significant pulmonary hypertension regardless of etiology had a prominent mid-systolic outward movement of the precordium which was absent in patients with right ventricular flow loads without pulmonary hypertension. Thus the kinetocardiogram (K_2 trace) qualitatively reflects the presence and aids in the separation of right ventricular flow loads from pressure loads.

4. From the studies presented it is concluded that the kinetocardiographic registration and probably precordial palpation are the most reliable methods of detecting abnormal right ventricular function.

Acknowledgment

We wish to express our sincere appreciation to Drs. Robert P. Grant and Tinsley R. Harrison for their helpful criticisms and suggestions in the preparation of this manuscript.

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Estimation of Pulmonary Artery Pressure and Pulmonary Vascular Resistance from Ultra Low Frequency Precordial Movements (Kinetocardiograms)*

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Kinetocardiographic criteria for the separation of right ventricular pressure loads from flow loads were presented in a previous paper.[1] The suggestion was made that the kinetocardiogram may offer some quantitative indication of the level of pulmonary artery pressure. The present study was undertaken to delineate this relationship.

Technics

Kinetocardiograms (low frequency precordial displacement movements) were recorded by the method previously presented.[1-3] Right heart catheterization was performed by the usual procedure. A Statham P23A or D transducer was used in recording the pulmonary artery pressure. The mean pressure was usually obtained electrically; however, in a few instances it was calculated by adding 42 per cent of the pulse pressure to the diastolic pressure. In a large series in which the mean pressure was determined by planimetry this calculation was found sufficiently close to justify its use.[4] Cardiac output was determined by the Fick principle. Total pulmonary vascular resistance was calculated by multiplying the mean artery pressure by 80 and dividing this by cardiac output (pulmonary blood flow in patients with left-to-right ventricular shunts) in liters per minute. The resultant figure is expressed in dynes seconds centimeters^{-5}. Correction for body size is achieved by dividing this by the surface area. It should be noted that the vascular resistance is different from pulmonary arteriolar resistance in that the mean capillary pressure (an estimation of left atrial or pulmonary venous pressure) is not subtracted from the mean pulmonary artery pressure in the former. This type of calculation for vascular resistance was chosen, since this probably represents more closely the total load on the right ventricle. Pulmonary blood flow was used in the calculations for pulmonary resistance rather than systemic flow in patients with left-to-right intracardiac shunts. Pulmonary blood flow was estimated by the formula

$$P.B.F. = \frac{O_2 \text{ Consumption}}{\text{Pulmonary venous oxygen content (95 per cent capacity)} - \text{Pulmonary artery oxygen content.}}$$

The kinetocardiogram was usually taken within a few days of the heart catheterization; however, in a few instances the records were a week or so apart.

Clinical Material: The seventy-four patients in the present study were unselected. Obviously only those were included in whom both kinetocardiograms and right heart catheterizations were performed. The series is comprised of thirty-four patients with mitral stenosis, thirteen patients with atrial septal defect, and twenty-seven patients with various lesions of the heart, including ventricular septal defect, patent ductus, isolated pulmonary hypertension and aortic valvular lesions, and a few in whom intracardiac shunts were suspected but were found to have normal catheterization measurements as well as a few normal subjects. The cardiac catheterization data from all of the patients were not complete, as the procedure was undertaken in some patients to obtain specific information. However, the kinetocardiogram was correlated with mean pulmonary artery pressure in all seventy-four patients, with pulmonary vascular resistance in sixty-one patients and with pulmonary vascular resistance corrected for body surface area in forty-seven patients.

Kinetocardiographic Analysis: A previous study indicated it was possible qualitatively to separate from

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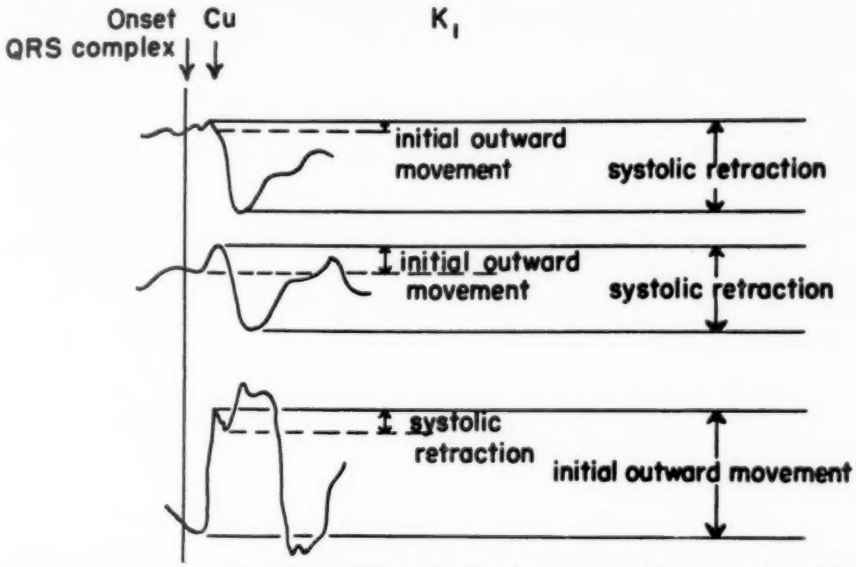

FIG. 1. Drawings to illustrate the method used in determining the kinetocardiographic ratio, as discussed in the text. These are traced from kinetocardiograms and are not free hand drawings. All three kinetocardiograms are taken from the V_1 position and labeled K_1. The arrow labeled "Cu" marks the onset of ejection as determined by the upstroke in the carotid pulse. Note that after the P wave, just before the QRS contraction, there are small movements which are more apparent in the first example; however, about 0.04 second after the onset of the QRS complex there is an abrupt outward movement which is small in amplitude in the first trace but moderately exaggerated in the second and markedly exaggerated in the third trace. The baseline from which the amplitude of this early pre-ejection outward movement is measured is taken at the point where there is a sharp change in gradient (0.03 to 0.07 second after the onset of the QRS complex). The systolic retraction, as illustrated in the three examples, is measured from the peak of the early systolic outward movement to the point of maximum retraction during early ejection. The amplitude of the initial movement is divided by the retraction during ejection, as illustrated, to obtain the ratio. These three examples show a normal subject, a patient with a slightly exaggerated early systolic outward movement and a patient with a marked increase in the initial systolic outward movement.

normals and differentiate right ventricular pressure loads from flow loads. The determinations were based upon measurements from the $K_2(V_2)$ trace. Subsequently it was noted that the $K_1(V_1)$ trace offered a better quantitation as to pulmonary artery pressure than the K_2 trace. Hence, the traces from the lead V_1 precordial electrocardiographic position (labeled K_1) were used exclusively for measurement in this study. However, it should be pointed out that the K_2 trace is still useful in qualitatively separating left ventricular pressure from flow loads while the present study is concerned only with the estimation of pulmonary artery pressure and resistance.

The ratio presented in this study was obtained by dividing the amplitude of the initial pre-ejection outward movement by the retraction during early ejection (Fig. 1).* The identification of the point of onset of the early systolic outward movement may be difficult in a few patients, especially those in whom the movement is not exaggerated in amplitude. After the P wave and before the QRS complex there are often small forward and backward movements of the precordium as a result of the auricular contraction which may at times fuse with the early outward systolic movement. Usually a change in gradient occurs 0.03 to 0.07 second after the onset of the QRS complex so that it is possible to separate the outward movement due to the ventricular activity from the movements due to auricular activity. This is illustrated in Figure 1. The point where the change in gradient occurs is taken as the point from which the amplitude of the outward movement is measured. The retraction of the precordium is measured from the peak of the initial outward movement to the point of maximum retraction during early ejection (Fig. 1). All records were obtained during normal held expiration. At least five complexes were measured and averaged in all the patients, and in the few patients with auricular

* These movements were selected to determine the ratio because previous studies indicated the initial outward movement was related to right ventricular activity and the systolic retraction was related to cardiac output or stroke volume.[1]

TABLE I—Findings in Mitral Stenosis (Thirty-Four Cases)

Case No.	Mean Pulmonary Artery Pressure (mm. Hg)	Cardiac Output (L./min.)	Cardiac Index (L./min. M^2)	Pulmonary Vascular Resistance (dynes sec. $cm.^{-5}$)	Pulmonary Vascular Resistance (dynes sec. $cm.^{-5}/M^2$)	Kinetocardiographic Ratio
1	87	5.96	4.62	1,167	926	2.23
2	35	4.84	3.12	578	375	1.52
3	35	3.46	2.4	808	561	1.00
4	67	5.46	3.03	984	547	1.59
5	30	5.0	2.59	480	249	0.03
6	48	4.6	2.84	832	514	1.71
7	45	4.10	2.27	878	485	2.04
8	27	7.31	3.53	295	143	0.65
9	26	4.88	2.14	424	186	0.13
10	34	2.65	1.54	1,024	595	0.94
11	62	2.77	1.65	1,792	1,067	3.88
12	35	1.98	1.47	1,416	1,049	1.03
13	28	3.9	2.8	576	413	1.98
14	70	2.14	1.42	2,616	1,732	3.38
15	24	4.30	2.66	448	277	1.83
16	55	5.1	3.5	862	590	1.05
17	24	4.46	2.11	432	205	1.83
18	18	3.30	2.13	440	306	0.16
19	14	2.91	1.75	385	232	0.98
20	37	5.36	2.69	552	277	1.01
21	80	3.75	2.31	1,706	1,053	2.97
22	37	4.5	2.83	658	414	1.62
23	28	6.8	4.20	328	201	0.06
24	70	3.48	2.29	1,609	1,056	2.22
25	21	4.16	2.81	209	182	0.42
26	30	4.41	...	544	...	0.78
27	95	5.44	...	1,400	...	2.09
28	52	2.99	...	1,391	...	1.32
29	57	4.42	...	1,031	...	3.50
30	29	...	...	...	...	0.72
31	77	...	...	...	...	3.30
32	42	...	...	...	...	2.28
33	55	...	...	...	...	3.42
34	46	...	...	...	...	2.29

TABLE II—Findings in Atrial Septal Defect (Thirteen Cases)

Case No.	Mean Pulmonary Artery Pressure (mm. Hg)	Cardiac Output (L./min.)	Pulmonary Blood Flow (L./min.)	Pulmonary Blood Flow (L./min./M^2)	Pulmonary Resistance (dynes sec. $cm.^{-5}$)	Pulmonary Resistance (dynes sec. $cm.^{-5}/M^2$)	Kinetocardiographic Ratio
1	16	4.17	18.50	13.31	69	50	0.56
2	20	8.6	16.8	8.62	95	49	0.08
3	19	5.5	10.3	6.48	147	92	0.24
4	18	4.76	7.16	3.54	201	100	0.35
5	18	4.6	19.63	12.75	74	48	0.75
6	29	8.2	30.3	18.51	77	48	0.58
7	16	4.8	15.9	9.94	81	51	0.53
8	24	4.07	12.5	7.35	154	91	0.29
9	32	4.7	10.0	5.85	256	150	0.44
10	40	3.8	5.6	...	568	...	1.61
11	32	8.3	5.95	...	434	...	1.70
12	19	3.55	12.7	...	120	...	0.83
13	17	...	...	...	...	...	0.26

TABLE III—Findings in Miscellaneous Group

Case No.	Diagnosis*	Mean Pulmonary Artery Pressure (mm. Hg)	Cardiac Output (L./min.)	Cardiac Index (L./min./M²)	Pulmonary Blood Flow (L./min.)	Pulmonary Blood Flow (L./min./M²)	Pulmonary Resistance (dynes sec. cm.⁻⁵)	Pulmonary Resistance (dynes sec. cm.⁻⁵/M²)	Kinetocardiographic Ratio
1	ASHD	18	8.5	...	...	5.6	170	112	0.38
2	PD	62	4.22	...	13.45	7.82	368	214	0.26
3	Coarctation	11	12.2	7.63	...	...	7	4	0.23
4	VSD	19	7.77	5.05	...	...	195	127	0.56
5	N	11	6.2	3.6	...	...	142	83	0.11
6	VSD	17	5.7	3.39	15.76	9.38	86	51	0.63
7	IPH	53	4.8	2.50	...	...	883	460	1.65
8	PD	12	...	...	4.3	2.91	224	151	0.55
9	MI	14	4.9	3.27	...	...	229	153	0.29
10	N	10	7.47	4.24	...	...	107	61	0.02
11	ASHD	74	2.68	1.46	...	...	2,208	1,207	0.32
12	VSD	53	4.5	...	20.4	14.68	208	150	0.89
13	ASHD	18	5.2	3.67	...	...	291	205	0.26
14	Unk	16	4.8	3.0	...	...	266	...	0.44
15	N	14	4.6	...	...	...	343	...	0.18
16	VSD	16	4.09	...	6.61	...	194	...	0.06
17	N	12	5.5	...	...	...	174	...	0.25
18	VSD	44	2.31	...	4.43	...	794	...	0.86
19	AI	17	4.85	...	...	...	280	...	0.26
20	N	14	7.8	...	...	...	143	...	0.44
21	PD	15	...	...	...	...	...	...	0.27
22	AS	36	...	...	...	...	...	...	2.52
23	VSD	6	...	...	...	...	...	...	0.42
24	PD	23	...	...	...	...	...	...	0.10
25	PD	80	...	...	...	...	...	...	0.71
26	N	11	...	...	...	...	...	...	0.27
27	N	12	...	...	...	...	...	...	0.11

* N = Normal. ASHD = Arteriosclerotic heart disease. VSD = Ventricular septal defect. PD = Patent ductus. MI = Mitral insufficiency. AI = Aortic insufficiency. Unk = Undiagnosed heart disease. AS = Aortic stenosis. IPH = Isolated pulmonary hypertension.

fibrillation as many complexes as possible (usually ten) were measured.

Results

Table I presents the data from the thirty-four patients with mitral stenosis; Table II, the data from the thirteen patients with atrial septal defects and Table III, the data from the twenty-seven patients in the miscellaneous group. Figure 2 demonstrates the correlation of the mean pulmonary artery pressure to the ratio as obtained from the K_1 point. The coefficient of correlation in this instance is 0.70; the regression equation is $Y = 17.7 + 15.4X$, where Y is the pulmonary artery pressure and X is the ratio. The standard error of estimate (S_y) is 16. Note that the pulmonary artery pressure in this series of patients is always above a mean of 30 mm. Hg when the ratio is 2 or greater.

Figure 3 presents the correlation of the ratio with the vascular resistance. Note the correlation coefficient in this instance is 0.77; the regression equation is $Y = 86.3 + 559.3X$ and the standard error (S_y) is 399. From the graph it can be noted that the vascular resistance is above 400 dynes second cm.$^{-5}$ when the ratio is above 1 and above 900 when the ratio is 2 or greater.

Figure 4 presents the correlation of the ratio with the vascular resistance corrected for surface area. In this instance the coefficient of correlation is 0.73. The regression equation is $Y = 71.5 + 301.6X$ and the standard error (S_y) is 253. Again the vascular resistance per meter second is significantly elevated (above 900) where the ratio is above 2:1. Note that by correcting the vascular resistance for surface area the scatter is reduced somewhat, although the coefficient of correlation is less than that obtained

TABLE I—Findings in Mitral Stenosis (Thirty-Four Cases)

Case No.	Mean Pulmonary Artery Pressure (mm. Hg)	Cardiac Output (L./min.)	Cardiac Index (L./min. M^2)	Pulmonary Vascular Resistance (dynes sec. cm.$^{-5}$)	Pulmonary Vascular Resistance (dynes sec. cm.$^{-5}/M^2$)	Kinetocardiographic Ratio
1	87	5.96	4.62	1,167	926	2.23
2	35	4.84	3.12	578	375	1.52
3	35	3.46	2.4	808	561	1.00
4	67	5.46	3.03	984	547	1.59
5	30	5.0	2.59	480	249	0.03
6	48	4.6	2.84	832	514	1.71
7	45	4.10	2.27	878	485	2.04
8	27	7.31	3.53	295	143	0.65
9	26	4.88	2.14	424	186	0.13
10	34	2.65	1.54	1,024	595	0.94
11	62	2.77	1.65	1,792	1,067	3.88
12	35	1.98	1.47	1,416	1,049	1.03
13	28	3.9	2.8	576	413	1.98
14	70	2.14	1.42	2,616	1,732	3.38
15	24	4.30	2.66	448	277	1.83
16	55	5.1	3.5	862	590	1.05
17	24	4.46	2.11	432	205	1.83
18	18	3.30	2.13	440	306	0.16
19	14	2.91	1.75	385	232	0.98
20	37	5.36	2.69	552	277	1.01
21	80	3.75	2.31	1,706	1,053	2.97
22	37	4.5	2.83	658	414	1.62
23	28	6.8	4.20	328	201	0.06
24	70	3.48	2.29	1,609	1,056	2.22
25	21	4.16	2.81	209	182	0.42
26	30	4.41	...	544	...	0.78
27	95	5.44	...	1,400	...	2.09
28	52	2.99	...	1,391	...	1.32
29	57	4.42	...	1,031	...	3.50
30	29	...	...	...	...	0.72
31	77	...	...	...	...	3.30
32	42	...	...	...	...	2.28
33	55	...	...	...	...	3.42
34	46	...	...	...	...	2.29

TABLE II—Findings in Atrial Septal Defect (Thirteen Cases)

Case No.	Mean Pulmonary Artery Pressure (mm. Hg)	Cardiac Output (L./min.)	Pulmonary Blood Flow (L./min.)	Pulmonary Blood Flow (L./min./M^2)	Pulmonary Resistance (dynes sec. cm.$^{-5}$)	Pulmonary Resistance (dynes sec. cm.$^{-5}/M^2$)	Kinetocardiographic Ratio
1	16	4.17	18.50	13.31	69	50	0.56
2	20	8.6	16.8	8.62	95	49	0.08
3	19	5.5	10.3	6.48	147	92	0.24
4	18	4.76	7.16	3.54	201	100	0.35
5	18	4.6	19.63	12.75	74	48	0.75
6	29	8.2	30.3	18.51	77	48	0.58
7	16	4.8	15.9	9.94	81	51	0.53
8	24	4.07	12.5	7.35	154	91	0.29
9	32	4.7	10.0	5.85	256	150	0.44
10	40	3.8	5.6	...	568	...	1.61
11	32	8.3	5.95	...	434	...	1.70
12	19	3.55	12.7	...	120	...	0.83
13	17	...	...	...	...	...	0.26

TABLE III—Findings in Miscellaneous Group

Case No.	Diagnosis*	Mean Pulmonary Artery Pressure (mm. Hg)	Cardiac Output (L./min.)	Cardiac Index (L./min./M²)	Pulmonary Blood Flow (L./min.)	Pulmonary Blood Flow (L./min./M²)	Pulmonary Resistance (dynes sec. cm.⁻⁵)	Pulmonary Resistance (dynes sec. cm.⁻⁵/M²)	Kinetocardiographic Ratio
1	ASHD	18	8.5	...	...	5.6	170	112	0.38
2	PD	62	4.22	...	13.45	7.82	368	214	0.26
3	Coarctation	11	12.2	7.63	...	...	7	4	0.23
4	VSD	19	7.77	5.05	...	...	195	127	0.56
5	N	11	6.2	3.6	...	...	142	83	0.11
6	VSD	17	5.7	3.39	15.76	9.38	86	51	0.63
7	IPH	53	4.8	2.50	...	...	883	460	1.65
8	PD	12	...	...	4.3	2.91	224	151	0.55
9	MI	14	4.9	3.27	...	...	229	153	0.29
10	N	10	7.47	4.24	...	...	107	61	0.02
11	ASHD	74	2.68	1.46	...	..	2,208	1,207	0.32
12	VSD	53	4.5	...	20.4	14.68	208	150	0.89
13	ASHD	18	5.2	3.67	...	...	291	205	0.26
14	Unk	16	4.8	3.0	...	...	266	...	0.44
15	N	14	4.6	...	...	...	343	...	0.18
16	VSD	16	4.09	...	6.61	...	194	...	0.06
17	N	12	5.5	...	...	...	174	...	0.25
18	VSD	44	2.31	...	4.43	...	794	...	0.86
19	AI	17	4.85	...	...	...	280	...	0.26
20	N	14	7.8	...	...	...	143	...	0.44
21	PD	15	...	...	...	...	...	...	0.27
22	AS	36	...	...	...	...	...	...	2.52
23	VSD	6	...	...	...	...	...	...	0.42
24	PD	23	...	...	...	...	...	...	0.10
25	PD	80	...	...	...	...	...	...	0.71
26	N	11	...	...	...	...	...	...	0.27
27	N	12	...	...	...	...	...	...	0.11

* N = Normal. ASHD = Arteriosclerotic heart disease. VSD = Ventricular septal defect. PD = Patent ductus. MI = Mitral insufficiency. AI = Aortic insufficiency. Unk = Undiagnosed heart disease. AS = Aortic stenosis. IPH = Isolated pulmonary hypertension.

fibrillation as many complexes as possible (usually ten) were measured.

Results

Table I presents the data from the thirty-four patients with mitral stenosis; Table II, the data from the thirteen patients with atrial septal defects and Table III, the data from the twenty-seven patients in the miscellaneous group. Figure 2 demonstrates the correlation of the mean pulmonary artery pressure to the ratio as obtained from the K_1 point. The coefficient of correlation in this instance is 0.70; the regression equation is $Y = 17.7 + 15.4X$, where Y is the pulmonary artery pressure and X is the ratio. The standard error of estimate (S_y) is 16. Note that the pulmonary artery pressure in this series of patients is always above a mean of 30 mm. Hg when the ratio is 2 or greater.

Figure 3 presents the correlation of the ratio with the vascular resistance. Note the correlation coefficient in this instance is 0.77; the regression equation is $Y = 86.3 + 559.3X$ and the standard error (S_y) is 399. From the graph it can be noted that the vascular resistance is above 400 dynes second cm.$^{-5}$ when the ratio is above 1 and above 900 when the ratio is 2 or greater.

Figure 4 presents the correlation of the ratio with the vascular resistance corrected for surface area. In this instance the coefficient of correlation is 0.73. The regression equation is $Y = 71.5 + 301.6X$ and the standard error (S_y) is 253. Again the vascular resistance per meter second is significantly elevated (above 900) where the ratio is above 2:1. Note that by correcting the vascular resistance for surface area the scatter is reduced somewhat, although the coefficient of correlation is less than that obtained

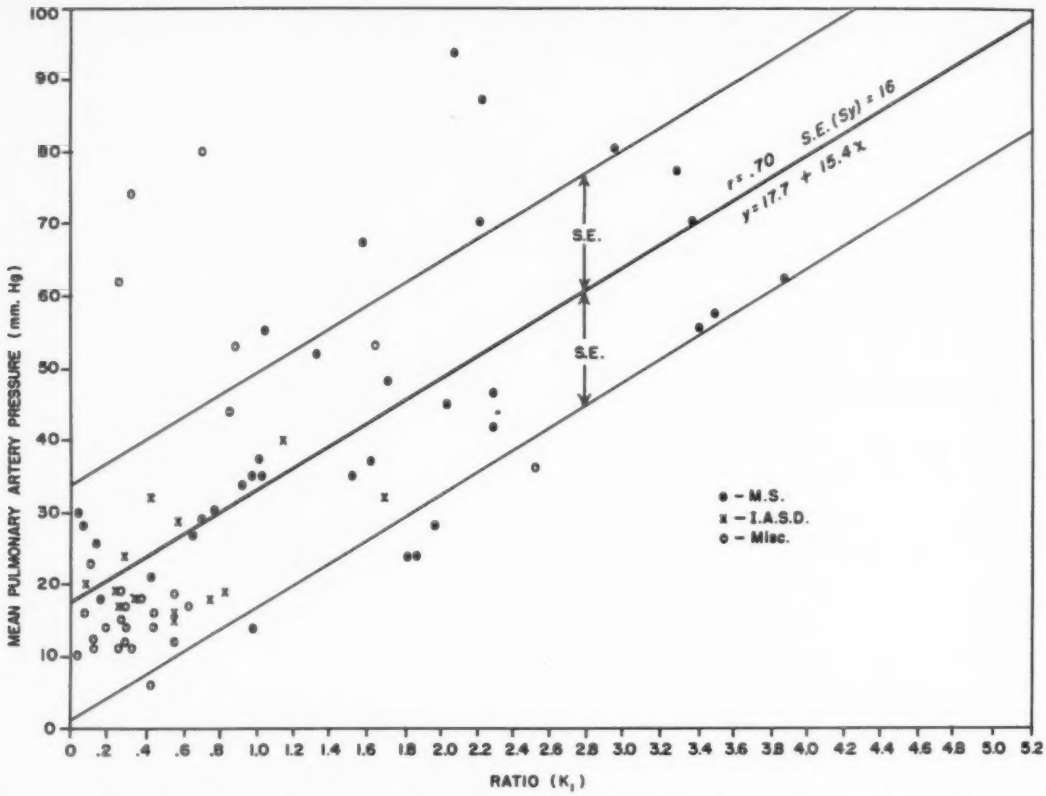

FIG. 2. Scattergram depicting the correlation between mean pulmonary artery pressure and the ratio obtained from the K_1 kinetocardiographic trace. The "r" as listed is the coefficient of correlation; the equation represents the regression equation for the data, where Y is the pulmonary artery pressure and X is the kinetocardiographic ratio. The standard error of estimate (S_y) is also listed. One standard error of the regression equation is represented by the lines on each side of the regression line. Note that the pulmonary artery pressure was always above a mean of 30 mm. Hg in these patients when the kinetocardiographic ratio was 2 or greater.

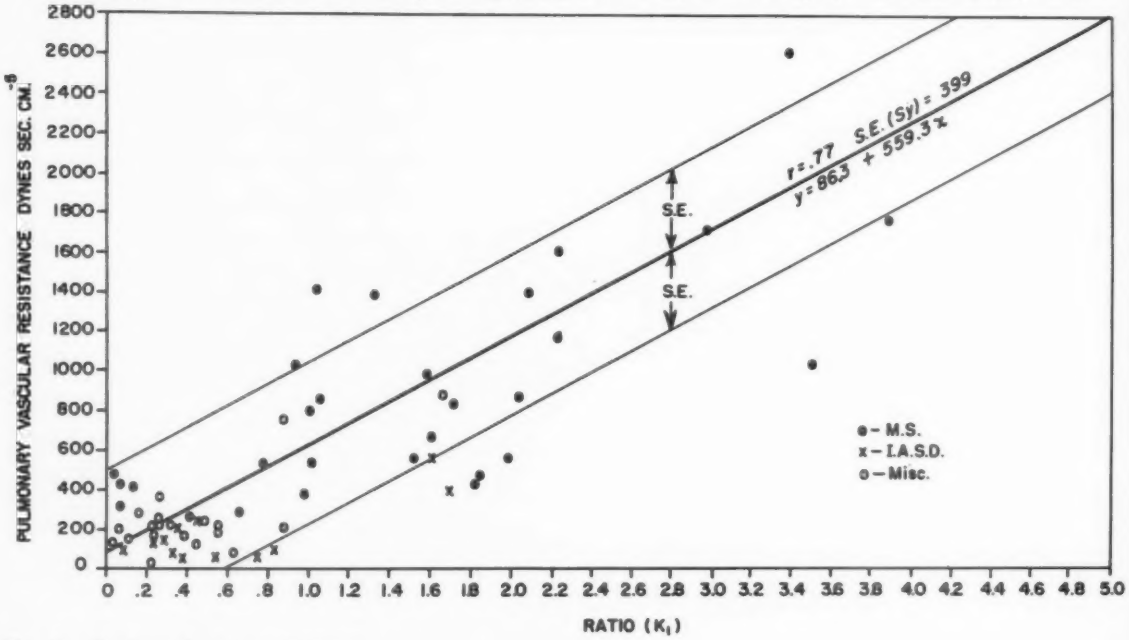

FIG. 3. See legend on opposite page.

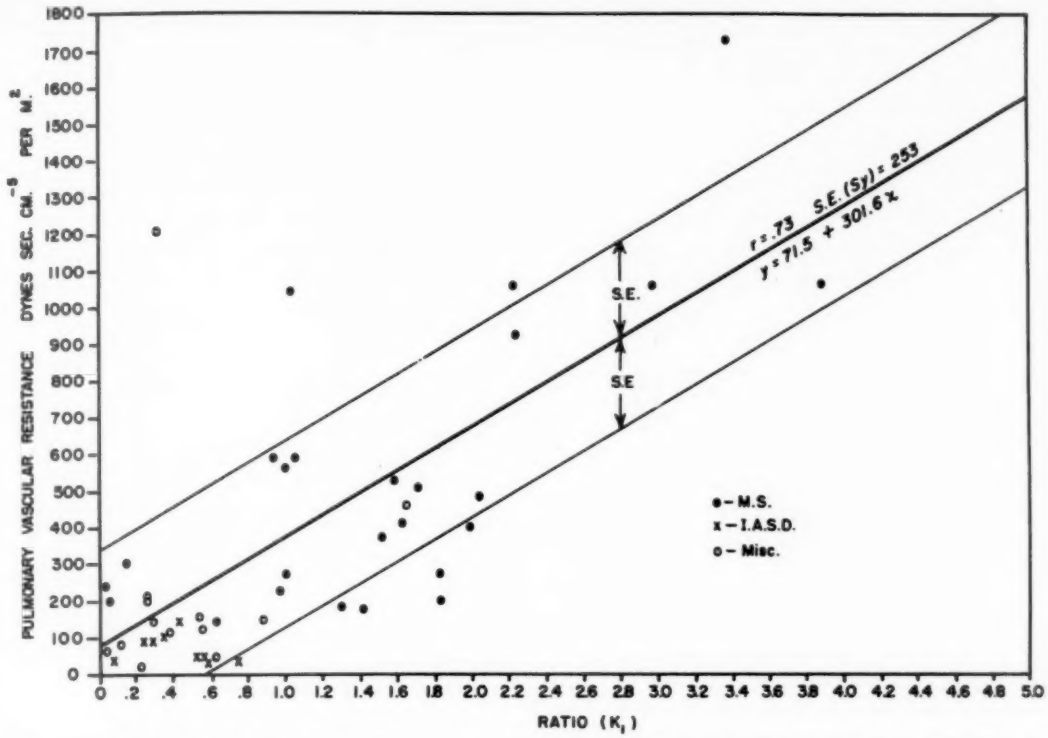

FIG. 4. Correlation of the pulmonary vascular resistance corrected for surface area with the kinetocardiographic ratio. The coefficient of correlation (r) is 0.73; the regression equation is $Y = 71.5 + 301.6X$ where Y equals the pulmonary vascular resistance per sq. meter and X is the kinetocardiographic ratio. The standard error of estimate (S_y) is 253 and one standard error is represented by the lines on each side of the regression equation. Vascular resistance per meter second is significantly elevated (above 900 dynes where the ratio was 2:1 or greater). The vascular resistance when corrected for surface area reduces the scatter somewhat; however, the coefficient of correlation was reduced as well. This is probably due to the fact that there are fewer observations in this group than that used in the previous graph.

for vascular resistance alone. This is probably due to the fact that there are less observations in this group of patients.

COMMENTS

It is apparent from Figures 2, 3 and 4 that there is a significant correlation of the ratio obtained from the kinetocardiographic $K_1(V_1)$ trace with the pulmonary artery pressure, vascular resistance and vascular resistance corrected for surface area. The scatter is somewhat large in all three instances, as manifested by the standard error (S_y); however, the degree of scatter is lessened by correcting the vascular resistance for surface area. Nevertheless, the entire relationships are much better than was anticipated, as the kinetocardiograms were obtained under different conditions than the catheterizations and on different days. In addition, only one point over the precordium was taken to estimate the ratio and it is possible that traces from other areas, such as those from the right parasternal region in the third or the fifth intercostal space, may actually be superior. As these traces were not uniformly available, only one position was selected for the present study.

The correlation apparently holds for a fairly wide group of patients with different types of

FIG. 3. Correlation of the pulmonary vascular resistance with the ratio obtained from the K_1 kinetocardiographic trace. The coefficient of correlation (r) is 0.77 and the regression equation is $Y = 86.3 + 559.3X$ where Y is the pulmonary vascular resistance and X is the kinetocardiographic ratio. The standard error of estimate is 399 and one standard error is represented by the two lines on each side of the regression equation. It can be noted from the graph that the vascular resistance was above 400 dynes second cm.$^{-5}$ when the ratio was above 1 and above 900 when the ratio was 2 or greater.

heart diseases. However, it should be pointed out that patients with anatomic changes of the chest wall, such as associated with pulmonary emphysema or kyphoscoliosis, were not included in the present study, as these patients are not routinely catheterized. In addition these correlations probably do not apply to patients with pulmonic stenosis since the calculations would have to be related in some other fashion to valvular resistance rather than pulmonary vascular resistance.

Summary and Conclusions

1. Right heart catheterization findings were correlated with a ratio obtained from kinetocardiographic traces (low frequency precordial movements) in a group of seventy-four patients with various types of heart disease. The ratio was obtained from the $K_1(V_1)$ trace by dividing the amplitude of the initial outward systolic movement by the retraction during early ejection. When this ratio is compared to the mean pulmonary artery pressure the coefficient of correlation (r) is 0.70 and when compared to the pulmonary vascular resistance the coefficient of correlation (r) is 0.77.

2. The findings indicate that it is possible to make a reasonably accurate estimate of mean pulmonary artery pressure and pulmonary vascular resistance from the kinetocardiogram in most instances. Whether or not these relationships apply to patients with pulmonary emphysema, deformity of the chest wall or in patients with congenital heart disease in whom there is an abnormal relationship of the chambers of the heart to the chest wall, remains to be determined.

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Low Frequency Tracings of Precordial Displacement and Acceleration

Technical Comparison of Various Systems*

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IN THE PAST, different workers in ballistocardiography observed certain similarities between ballistic tracings and other pulsatory records. On the other hand, many of them published studies on the low frequency tracings of the chest wall and noticed their similarity to ballistocardiograms. This study was undertaken in order to investigate the role of instrumental influences on the pattern and timing of the precordial pulsatory vibrations.

In ballistocardiography, as well as in precordial cardiography, multiple attempts at clinical application have been considerably retarded by the lack of consistently reproducible oscillatory patterns. Tracings recorded by different methods could not always be compared with each other, and no generally accepted physiologic standards exist in either method. In our study, certain procedures, including filtration of the precordial vibrations, will be investigated and a comparison made between the various systems. The time relationship of the various waves will be studied by comparing the patterns recorded with different methods of filtration and different pick-ups with those of the ballistocardiographic patterns. The physical conditions of standardization will be examined.

METHODS

The precordial vibrations have been studied in six adult men, from those areas which are used for recording the V_E, V_3 and V_4 electrocardiographic leads. The subjects were in the supine position. The records were taken in expiratory apnea.

Five different types of pick-up have been employed: (1) a pressure capacitance diaphragm pick-up with an ionization transducer tube;† (2) a capacitance microphone;‡ (3) the ballistocardiographic device of Arbeit-Lindner[1] applied to the thorax; (4) a crystal microphone with linear response (Sanborn) and (5) an electromagnetic transducer with a frequency response proportional to acceleration in the 2 to 30 c.p.s. band.[2,3] These devices were applied by either a suction cup or direct contact, but avoided any pressure. The tracings were recorded by using filters in the following frequency bands: 0.01 to 100; 0.01 to 5; 0.01 to 20; 0.01 to 50; 4 to 20; 5 to 20; 12 to 20 and 5 to 25 c.p.s.; these tracings have been recorded simultaneously with electrocardiogram, phonocardiogram or arterial pulses. Either RC filters or electronic band pass filters were used, as described in previous studies from this laboratory.[4] Simultaneous displacement, velocity and acceleration tracings were further recorded by the Arbeit-Lindner device, either with or without additional filtration. Data concerning time measurements have been based on the average values of fifteen consecutive cycles.

RESULTS

OSCILLATORY PATTERNS

The oscillatory pattern of precordial tracings has been found to depend on the physical characteristics of the pick-up–amplifier-filter system. Other factors being equal, the filter band seemed to determine the configuration of the precordial tracing. No significant difference in pattern has been observed between tracings taken from areas designated as V_E, V_3 and V_4. Different oscillatory *displacement* patterns were obtained in the 0.01 to 100 c.p.s. band by the use of the

† Manufactured by the Decker Corporation, Bala Cynwyd, Pennsylvania.

‡ Manufactured by the Altec Corporation, Beverly Hills, California.

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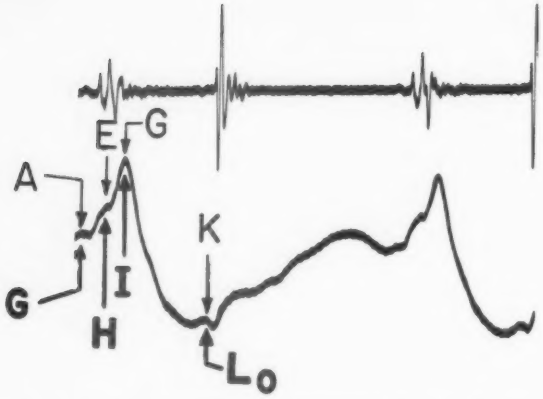

FIG. 1. The precordial displacement tracing in the 0.01 to 100 c.p.s. frequency band. Normal male (twenty-four years old). From above: Phonocardiogram (frequency band 60 to 120). Displacement tracing (Decker capacitance pick-up plus filter). The pattern is similar to the mirror image of an ultra low frequency displacement ballistocardiogram. Bold letters: ballistocardiographic nomenclature.

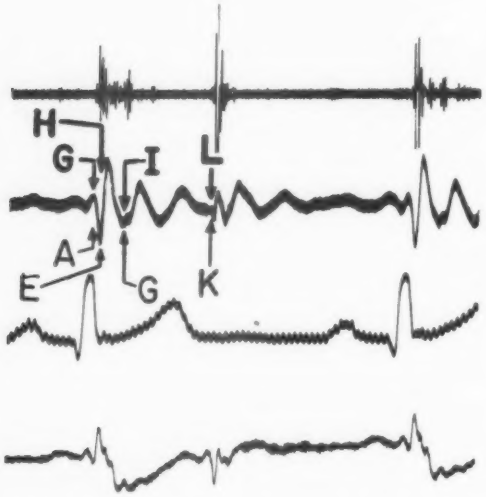

FIG. 2. Precordial acceleration tracing. Normal young adult (thirty-three years old). From above: Phonocardiogram in the 60 to 120 c.p.s. band at apex. Acceleration tracing; electromagnetic pick-up (Rosa) without additional filtration. Electrocardiogram. Precordial displacement at apex (linear microphone).

linear (Fig. 2), the capacitance (Fig. 1) or the electromagnetic (Fig. 5, A) transducer. These differences seem due to the frequency response of the pick-up and underline the importance of the use of pick-ups with well known physical characteristics.

In the 5 to 25 c.p.s. range, no difference in pattern has been found between capacitance (*displacement*) or electromagnetic (*acceleration*)

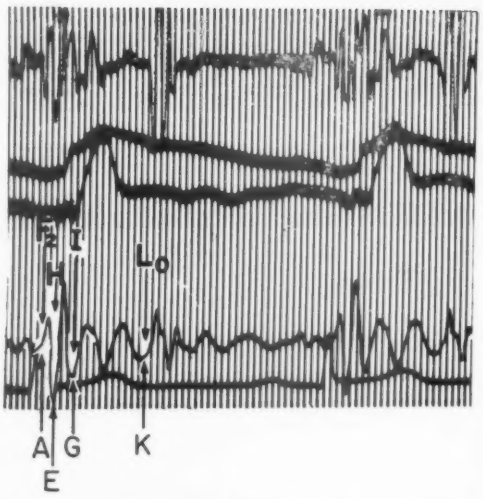

FIG. 3. Precordial "displacement" tracing in the 5 to 25 c.p.s. band. Normal male (twenty-five years old). From above: Phonocardiogram (50 to 100 c.p.s. band). Carotid tracing. Tracing of abdominal aorta (4 to 20 c.p.s. band). Precordial "displacement" (Altec capacitance microphone, filter 5–25 c.p.s. band). Electrocardiogram. Time, 0.02 sec. The pattern is similar to that of the ultra low frequency acceleration (lateral) ballistocardiogram. Bold letters: ballistocardiographic nomenclature.

transducers (Figs. 2 and 3). Tracings recorded by the use of the electromagnetic acceleration transducer showed identical patterns in the 5 to 25 c.p.s. and in the unfiltered 2 to 30 c.p.s. band.

The following relationships to certain ballistocardiographic patterns were established:

A. Precordial Displacement: (1) Precordial displacement in the 0.01 to 100 c.p.s. band (Fig. 1). This pattern is similar to the mirror image of an *ultra low-frequency displacement ballistocardiogram* and appears on tracings recorded with the capacitance transducer with ionization tube. (2) Precordial displacement in the 5 to 25 c.p.s. band (Fig. 3.) This pattern is similar to that of the *ultra low frequency acceleration* (*head-foot or lateral ballistocardiogram*) (see also Fig. 2). (3) Precordial displacement in the 12 to 20 c.p.s. band (Fig. 4, B). It is similar to the *direct body acceleration ballistocardiogram.*

B. Precordial Velocity: In the 0.01 to 100 c.p.s. band (Fig. 4,A) there is practically no difference between this pattern and that of the *ultra low frequency velocity ballistocardiogram.* It may be reproduced by the use of both types of electromagnetic transducers.

C. Precordial Acceleration: (1) Precordial

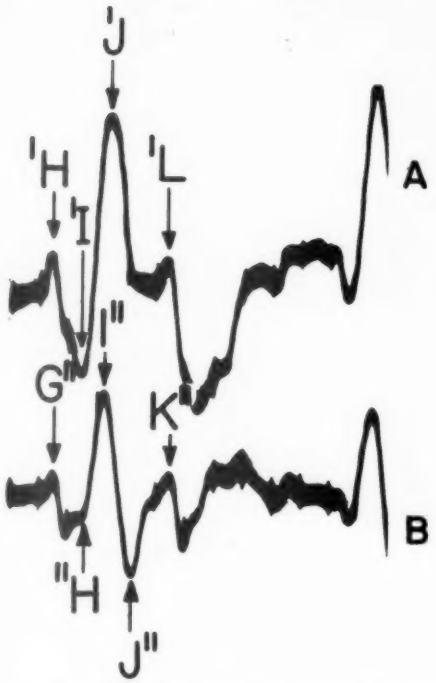

FIG. 4. Simultaneously recorded precordial tracing, (velocity and displacement). Normal young adult (twenty years old). From above: Precordial velocity tracing (Arbeit-Lindner pick-up plus 0.01 to 100 c.p.s. filter). Precordial displacement (Arbeit-Lindner pick-up plus 12 to 20 c.p.s. filter). Time, 0.10 sec. The pattern is similar to that of the direct body ballistocardiogram.

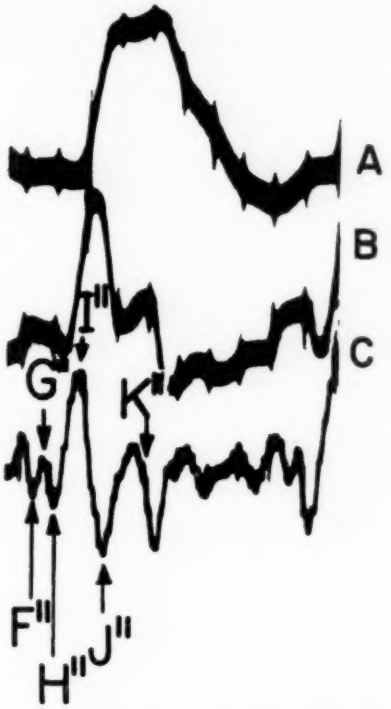

FIG. 5. Simultaneous precordial displacement, velocity and acceleration records. Normal young adult (twenty years old). Pick-up: Arbeit-Lindner without additional filtration (0.01 to 100 c.p.s.). From above: displacement, velocity, acceleration. The pattern of the "unfiltered" precordial acceleration is similar to that of the high frequency ballistocardiogram. Note the effect of filtration on this pattern (compare with Fig. 2). Time, 0.10 sec.

acceleration in the 0.01 to 100 c.p.s. band (Fig. 5, C). This pattern is similar but not identical to the high frequency ballistocardiogram. (2) Precordial acceleration in the 5 to 25 c.p.s. band (Fig. 2). This pattern resembles the *ultra low frequency acceleration ballistocardiogram* (Fig. 3 and Table I).

Thus, there is no difference in pattern between precordial acceleration and precordial displacement in the 5 to 25 c.p.s. band. Table I lists the various filtered precordial tracings and compares them with different types of ballistocardiograms or other precordial tracings. The patterns presented in the figures were reproduced in the same subjects repeatedly through several months.

Any change of either the high or low cut-off filter, or both, resulted in consecutive changes in the oscillatory patterns. Accordingly, in these cases the similarity to the *ballistocardiogram* was less evident and a constant pattern was not maintained.

TIME MEASUREMENTS

The configuration of the precordial tracing in the 5 to 25 c.p.s. band has been widely discussed in previous reports.[3,17] All oscillations, then, were labeled by letters in alphabetical order from A through O. In this study, some peaks and troughs have been labeled by two letters each. The letters in *bold* type correspond to those suggested by the Committee of the American Heart Association on Ballistocardiographic Terminology;[18] the letters in *fine* type are in accordance with the nomenclature used in previous reports. The symbols permit the measurement of time intervals related to either the Q wave of the electrocardiogram or the heart sounds. The only peaks and troughs which have been labeled are those indicating similar intervals with those published on ultra low frequency acceleration ballistocardiograms by Scarborough and his group.[6]

TABLE I

Comparison of Filtered Precordial Tracings with Other Precordial and Ballistocardiographic Records

	Frequency Range (c.p.s.)	Pick-up	Similarity of Pattern to Other Precordial or Ballistocardiographic Tracings
Precordial displacement....	0.01–100	Capacitance (Decker) (Fig. 1)	Ultra low frequency displacement ballistocardiogram[5,6] Kinetocardiogram apical region[7] Second integral of thoracic acceleration[8] Thoracic displacement[9]* Precordial low frequency tracings[10]
	5–25	Capacitance (Altec) (Fig. 3)	Precordial acceleration[2] Acceleration ballistocardiogram[11] Ultra low frequency (lateral) acceleration ballistocardiogram[4] Precordial acceleration[12] Ballistocardiogram acceleration[13] Precordial force-thrust and acceleration ballistocardiogram[14]
	12–20	Electromagnetic (Arbeit) (Fig. 4)	Direct body acceleration[15]
Precordial velocity.....	0.01–100	Electromagnetic (Arbeit) (Fig. 4)	Ultra low frequency velocity ballistocardiogram[6]
Precordial acceleration.....	0.01–100	Electromagnetic (Arbeit) (Fig. 5)	High frequency ballistocardiogram[16]
	5–25 (2–30)	Electromagnetic (Rosa) (Fig. 2)	See precordial displacement 5–25 c.p.s. range

* Remote, contactless registration (U.S.A. Patent No. 2,352,011 [1940]).

Table II shows a comparison between signals and time relations of precordial tracings and various other methods. This table also contains the symbols used by Eddleman and his group[7], and permits the comparison of different methods not only in regard to patterns but also in regard to time intervals.

Comments

Mathematical relationship between pulsatile and ballistic phenomena has been observed and described by several authors.[19–21] Integration of thoracic accelerograms,[8] differentiation of thoracic displacement,[2] differentiation of carotid displacement,[22] and differentiation of constructed[23] or recorded plethysmograms[21,24,25] result in oscillatory patterns corresponding to the different aspects of the ballistic movements and provide evidence for common factors in the production of both regional and total body mass vibrations.

Little is known about the underlying physiological events causing precordial or ballistocardiographic oscillations. Vibrations recorded by one or the other of these methods may or may not have identical physiological meaning. The effect of filtration, probably similar to that of integration or differentiation, accentuates some common features of the tracings which have been repeatedly recorded by various investigators, and it seems that these patterns are fundamental. In this study the multitude of patterns recorded by different methods was reduced to three consistent types, by recording displacement, velocity or acceleration tracings in those frequency bands presenting patterns which resemble the respective ultra low frequency ballistocardiograms. A simplified standardization may be attempted by selecting two bands: (1) the 0.01 to 100 c.p.s. band for displacement and velocity and (2) the 5 to 25 c.p.s. band for displacement and acceleration. These data refer to the use of the capacitance pick-up with ionization tube for recording *displacement;* that of the electromagnetic (Arbeit-Lindner) pick-up for recording *velocity;* and to

TABLE II

Terminology and Time Relationship of Various Waves Recorded Through Various Methods

	American Heart Association Committee on Ballistocardiographic Terminology (Scarborough and Talbot) (Acceleration in Young Males)	Rosa and Luisada	Eddleman and Co-workers	Coincidence with Cardiovascular Events
Symbol and mean time distance from the Q wave of the electrocardiogram (msec.)	F_2 (G) 48	A 45	I_1	Onset of 1st heart sound; slow rise of right ventricular pressure (Rosa, 1958)
	H 100	E 94	I_4	20 msec. before carotid upstroke (Reeves and co-workers, 1957); upstroke of C wave on jugular phlebogram (Rosa and co-workers, 1955); rapid rise of right ventricular pressure (Rosa and Bender, 1958)
	I 153	G 164	E_1	Peak of C wave on jugular phlebogram (Rosa and co-workers, 1955); anacrotic shoulder of carotid acceleration (Rosa, 1955; Reeves, 1957); upstroke of abdominal aortic pulse (Rosa and Luisada, 1959)
	L_0 390	K 375	E_4	Second heart sound; incisura of pulmonary artery pressure curve (Rosa and Bender, 1958); ventricular relaxation (Hollis, 1958)

that of the electromagnetic pick-up with a frequency response proportional to *acceleration*.

The double terminology of the individual oscillations as presented in this study permits an arbitrary division of the cardiac cycle like that suggested by one of us in 1948,[2,3] and similar to that described by Eddleman et al.[7] and others.[12] The signals A, E, G and K are easily related to cardiac events and may be identified in both the ultra low frequency and the 5 to 25 c.p.s. range tracings (Figs. 1 and 2).

The segment included between A and E probably includes the isometric phase of right and left ventricular systole. The segment E to G probably corresponds to the phase of rapid ventricular ejection (between the opening of the semilunar valves and the initial rise of the abdominal aortic pulse). The G to K segment includes the second part of ventricular ejection. K coincides in time with the onset of the second heart sound.

Peaks and troughs of vibrocardiographic tracings are time signals, arbitrarily chosen when selecting the frequency band. The use of standardized technics and conventional symbols, however, should facilitate further comparative studies of cardiovascular events reflected in oscillatory phenomena.

Summary

Low and ultra low frequency precordial vibrations from areas designated as V_E, V_3 and V_4 in conventional *electrocardiographic* chest leads have been studied by means of five different types of pick-up with RC or electronic band pass filters. Tracings of displacement, velocity and acceleration, recorded in various frequency bands between 0.01 and 100 c.p.s., were compared to different kinds of ballistocardiographic and precordial records. Of the various oscillatory patterns recorded by the different methods (different frequency bands, different pick-ups, and different locations on the wall of the chest), three consistent and reproducible patterns have been selected on the basis of their similarity to the ultra low frequency ballistocardiographic displacement, ultra low frequency ballistocardiographic velocity, or ultra low frequency ballistocardiographic acceleration tracings, respectively.

The displacement 0.01 to 100 c.p.s. band-pattern is similar to the mirror image of the

ultra low frequency displacement ballistocardiogram. The 5 to 25 c.p.s. band (acceleration) pattern is similar to that of the ultra low frequency lateral or head-foot acceleration ballistocardiogram. The precordial velocity tracing resembles the ultra low frequency velocity ballistocardiogram. Apart from similarity in patterns, the comparison was based also on time measurements related to the electrocardiogram and various pulse tracings.

This similarity between precordial and ballistic patterns reveals the basic importance of recording pulsatory vibrations as physically pure aspects of the movement caused by cardiocirculatory mechanisms. It further holds the promise that standardized technics may contribute to the elimination of the disturbing variety of ballistic and precordial tracings.

Acknowledgment

We wish to thank Dr. John Nickerson for his constructive criticism.

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Further International Efforts for Standardization of Phonocardiography

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PHONOCARDIOGRAPHY still suffers from lack of uniformity both in regard to apparatus and to interpretation of the tracings.

An International Committee on Standardization held two meetings in 1950 (First World Congress of Cardiology) and in 1953 (Meeting of Soc. Française de Cardiologie). The conclusions were published in 1955 (*Am. Heart J.*, 50: 82, 1955 and *Cardiologia*, Vol. 26, 1955). One suggestion (by Duchosal) gave instructions in regard to notation of the area of recording. Agreement was reached on the fact that the basic phono tracing should follow the curve of sensitivity of the human ear. However, the possibility of recording two other tracings was considered, one for lower frequencies and the other for higher frequencies. This obviously would require the use of [additional*] filters.

A third meeting was held in connection with the Second European Congress of Cardiology (Stockholm) in 1956 and the conclusions were published in the following year (*Am. Heart J.*, 54: 314, 1957). The criteria of phonocardiography were considerably enlarged and the use of several channels was advocated. Definition of the "nominal frequency" was given. Intervals of one octave between channels were considered advisable.

During the Third World Congress of Cardiology, held in Brussels, Belgium, in September 1958, several participants were again invited to hold a meeting dealing with technical problems of phonocardiography. Present at the meeting were twenty-eight cardiologists and electronic specialists from ten countries.† Dr. Kleyn was elected chairman. Dr. Holldack and Dr. Luisada took notes and planned an exchange of letters in order to agree on the text of the resolution to be adopted.

The representatives of the various countries agreed that it would be premature to establish definite frequency characteristics to be used in the construction of phonocardiographs. On the other hand, the subsequent discussion revealed the acceptance of the following points:

(1) It is necessary to use some type of filter in order to obtain relevant and clinically significant phonocardiographic tracings.

(2) If the frequency response given by microphone, amplifiers and recording units is *linear* (a highly desirable feature of any apparatus), the most important variable is represented by the filter or filters. The frequency response of all these parts, including filters, should be such as to give the desired response for each frequency.

(3) It would be desirable for each researcher to indicate in his publications the frequency characteristics of his filters in a uniform manner:

(a) When only a high-pass filter is used, the researcher should give a series of numbers, separated by fraction lines. The first number denotes the frequency at which the increase in amplitude reaches 10 per cent (or −20 db) of the maximum value. The second number indicates the slope reached at this point in db per octave.

Example: 140 (−20 db)/24

---

* We added this word because obviously no apparatus would record a curve similar to that of the ear without some method of electric or mechanical filtration.

† A. Alella, Italy
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K. J. Blumberger, Germany
A. Brand, Israel
Brandeis, Belgium
P. Cossio, Argentina
O. Fagnoni, Italy
E. von Ferroni, Germany
Fricke, Germany
Ch. Friedl and, Mexico
E. Gadermann, Germany
A. F. Hakmann, The Netherlands
H. Hartman, The Netherlands
K. Holldack, Germany
Jonas, Czechoslovakia
J. B. Kleyn, The Netherlands
C. Lian, France
D. H. Lewis, U.S.A.
A. Luisada, U.S.A.
V. McKusick, U.S.A.
G. Minot, France
F. A. Rodrigo, The Netherlands
Schaeder, Germany
F. Schwarzer, Germany
A. Stella, Italy
M. R. Testelli, Italy
van Vollenhoven, The Netherlands
G. Weber, The Netherlands

(b) When a band-pass filter is used, the researcher would indicate in the same way the frequency characteristics both for the high and the low pass filters; the figures of the two filters would be separated by a horizontal line.

Example: 140 (−20 db)/24 −500 (−20 db)/24

Obviously these indications cannot take into consideration the acoustic properties of the chest, even though a homogeneous, proportional transmission was admitted.*

Following this meeting, an exchange of letters took place between the following researchers: Dr. J. B. Kleyn in Holland; Dr. K. Holldack and Mr. F. Schwarzer in Germany; Drs. A. A. Luisada and Rudolf Zalter and Mr. H. G. Beenken in the United States. This correspondence was prompted by the observation that the foregoing description fails to indicate the most desirable characteristics of high-pass or band-pass filters having a "peaked circuit." Therefore, more than one point of the slope should be described.

The parties finally agreed that two points would be sufficient for such description, the −3 db and the −20 db point according to the formula:

$x_1(-20\text{ db})/y_1/x_2\ (3\text{ db}) - x_3(-3\text{ db})/x_4\ (-20\text{ db})/y_2$

where y_1 and y_2 indicate the steepness of the slopes, while x_1, x_2, x_3, and x_4 are four frequencies which should be named in the case of a band-pass filter.

The previous example should then be modified as follows:

140 (−20 db)/24/190 (−3 db) −
400 (−3 db)/500 (−20 *db*)/24.

Here 140 and 500 are the two manual settings used in a given case for taking the theoretical band 140 to 500. On the other hand, 190 and 400 are the points of the slope which are respectively reached at the −3 db points.

It is remarkable that such an agreement was reached by correspondence and without further personal contact. This indicates how close is now the position of several workers in various countries in regard to this problem.

On the other hand, it is unfortunate that the final notation has become somewhat complex for use in the legend to be placed below each figure producing a clinical phonocardiogram.

An alternative solution would be to publish in schematic form the typical curve of the filter. Then, each legend could simply indicate the figures of either the variable manual sets or the fixed filter channels.

This notation cannot be regarded as carrying the authority of the international meeting because the agreement was reached afterwards and only between some of the participants. However, it is hoped that further correspondence with the others will indicate whether or not any contrasting point of view is raised by either the participants or other cardiologists and engineers.

Another point which was discussed at the meeting in Brussels was the number and width of the frequency bands to be used. One point of view (presented by Mr. Minot) was that each band should encompass 5 octaves, as follows: 5–25; 25–125; 125–625; 625–3125. This was not accepted because (1) most of the clinically significant vibrations would be included in the third band and (2) the various bands are too wide for adequate selection and amplification of the most important vibrations. Instead, Luisada and Zalter suggested four bands of 1 octave each, as follows: 30–60; 60–120; 120–240; 240–480, with additional optional bands for special studies above and below those just indicated. This suggestion, which is consistent with the recommendations of the Committee on Standardization of 1956, met with wide acceptance. However, Dr. Holldack and several others prefer a more flexible formula which would leave each researcher free to select the most suitable bands.

A further point which was discussed is the desirable slope of filters. Both Mr. Schwarzer and Dr. Luisada indicated their preference for a slope of −24 db per octave or greater. A different viewpoint (Mr. Fagnoni) indicating preference for −12 db per octave was only based on the possibility of building a less expensive type of apparatus, and was not accepted by the cardiologists present at the meeting. In the opinion of Dr. Holldack, the slope of the lowest filters should be flatter than that of the others.

* It was originally admitted that the decrement of amplitude with increase of frequencies is based on the physical law of the square root of frequency (briefly called "the inverse law of the square"). Studies of Zalter, Hodara and Luisada (*Am. J. Cardiol.*, 4: 3, 1959) seem to prove that the decrement is greater, being between the square and the cubic roots of the frequency, due to summation of physical and physiological factors. Dr. Holldack agrees that this is the case.

End of Symposium on Phonocardiography (Aldo A. Luisada, Guest Editor). Parts I through IV appeared in the July through October issues, respectively.

Review

Persistent Left Superior Vena Cava*

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REPORTS describing the incidence of anomalies of the venous return to the heart have increased significantly in recent years. Specifically, the presence of a persistent anterior cardinal vein, frequently referred to as persistent left superior vena cava, has been observed more frequently because of the increasing frequency of diagnostic studies and cardiovascular surgery.

Until a few years ago, reports concerning the accidental discovery of a persistent left superior vena cava were limited to anatomy and pathology journals, this anomaly being considered more an anatomic curiosity and an embryologic derangement than a true clinical syndrome. However, the recent progress made in cardiovascular surgery, together with the renewed interest in the physiology of the circulation, has greatly changed this perspective.

The first accurate description of the development of the great anterior veins with eventual remnants of fetal structures found in adults was given by Marshall in 1850.[1] However, case reports of left superior vena cava go as far back as 1787[2] and 1798[3]. McCotter,[4] in 1916, collected 120 cases from the literature and added three of his own. In 1954 Winter[5] collected 174 cases from the literature and brought the total world cases to 204, including his own. A few additional cases have been presented since then.[6–11] We can, therefore, conclude that persistence of the left superior vena cava is one of the most frequent anomalies of the systemic venous return.

During the last four years we have had the opportunity of collecting in our laboratories 37 cases of left superior vena cava in which the diagnosis was made by cardiac catheterization and/or angiocardiography and was definitely established in the majority of cases either at time of surgery or at autopsy (Table I). The unusual technical and physiologic aspects associated with this anomaly necessitate a brief summary of the embryologic development of the venous return to the heart.

EMBRYOLOGY

During the very early stage of the embryologic development (second to third embryonic week), the cardiac tube receives at its caudal extremity three groups of veins: (1) the two vitelline veins, which collect the blood of the yolk sac and primitive gut; (2) the two umbilical veins, which collect the blood of the chorion and join the vitelline veins; and (3) the ducts of Cuvier or common cardinal veins which collect the blood of the embryo (Fig. 1).

The ducts of Cuvier derive from the fusion of the anterior cardinal veins with the posterior cardinal veins. The left and right anterior cardinal veins drain the venous blood from the cephalic region of the embryo. The two posterior cardinal veins drain the blood from the dorsal and caudal region of the trunk. These ducts converge behind the heart, opening in the sinus venosus which is in connection with the primitive atrium (second month of fetal life). Later, a transverse anastomosis is formed between the anterior cardinal veins, and the primitive symmetrical position of the cardinal veins is lost. This anastomotic vessel drains, with a continuously increasing flow, the blood from the left side of the head and from the left arm into the right duct of Cuvier. The right duct, therefore, increases considerably in diameter, whereas the left duct undergoes a progressive diminution in caliber,

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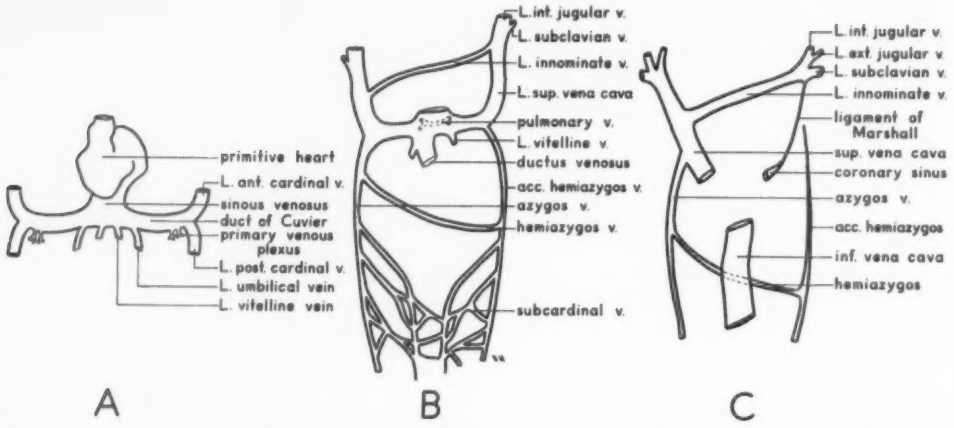


FIG. 1. Three successive stages of the embryologic development of the venous return to the heart.

losing connection with the cardinal veins. A second transverse connection is also formed between the two posterior cardinal veins through which the blood from the left posterior cardinal vein drains into the right posterior cardinal vein. The logical result of this process then is the atrophy of the major portion of the left posterior cardinal vein which loses its connection with the corresponding duct of Cuvier.

When the development is complete there will be a superior vena cava formed from the right duct of Cuvier and from the proximal portion of the right anterior cardinal veins below the newly formed transverse anastomosis. The distal portion of the right anterior cardinal vein, above the anastomosis, will form the right innominate vein. On the left, the proximal portion of what remains of the duct of Cuvier forms the coronary sinus, whereas the portion crossing the posterior wall of the left atrium will form the ligament of Marshall. The anastomotic tract between the two cardinal veins will form the left innominate vein to which will converge, just as on the right side, the left internal jugular and the left subclavian veins.

The embryologic evolution of the pulmonary venous system takes place simultaneously with the development of the systemic venous return. The primary venous plexus drains the area for the lung buds and empties through channels connected with the anterior cardinal veins. Gradually, during further stages, a median channel is formed between this venous plexus and the left atrium. This is the common pulmonary vein collecting the blood from both lungs. During the first half of the second embryonic month, this connecting channel is incorporated into the atrial wall. Its right and left tributary vessels, therefore, drain into the atrium through two separate orifices. This process of resorption continues up to the principal bifurcation of the left and right pulmonary veins. The ultimate arrangement is reached when the four pulmonary veins drain into the atrium with four separate orifices.[12–14]

Clinical Diagnosis

The mere presence of a left superior vena cava draining into the coronary sinus constitutes an anomaly which is not accompanied by any clinical symptomatology, inasmuch as the blood returns to the venous side of the systemic circulation and, therefore, does not result in any hemodynamic alteration.

In only 2 of our 37 cases, however, was the persistence of left superior vena cava found as an isolated feature. The presence of a left superior vena cava, consequently, is associated in the majority of cases with other congenital anomalies, as appears evident from the world literature as well as from the analysis of our own cases (35 of the total 37 cases studied) (Table I). The clinical, electrocardiographic, and radiologic features present are, then, those of the associated anomaly.

We believe that the presence of this anomalous vessel can be suspected from a careful examination of a standard roentgenogram of the chest and later confirmed through cardiac catheterization and angiocardiographic studies.

ROENTGEN OBSERVATIONS

Some investigators[15] have indicated that the presence of a left superior vena cava may be suggested by the enlargement of the base of the heart seen on fluoroscopy. This may be true in some

TABLE I

Summary of 37 Cases of Persistent Left Superior Vena Cava

Case No.	Name	Sex	Age (yr.)	Associated Congenital Anomalies	Status of Pulmonary Venous Return	Vascular Pedicle-Thoracic Ratio (%)
1.	S.G.	F	50	Atrial septal defect	—	28
2.	C.P.	F	10	Atrial septal defect	—	—
3.	E.T.	F	27	Atrial septal defect	—	33
4.	C.V.	F	31	Atrial septal defect	—	32
5.	J.C.	M	28	Atrial septal defect	—	21
6.	C.A.	F	7	Atrial septal defect, primum type	—	40
7.	R.L.	M	2	Atrial septal defect; dextroposition of heart	—	33
8.	B.J.	F	4	Atrial septal defect; dextroposition of heart	—	37
9.	I.S.	F	7 wk.	Atrial septal defect; ductus arteriosus	—	48
10.	M.F.	M	10	Atrial septal defect; pulmonic stenosis	—	—
11.	R.A.	M	21	Atrial septal defect; pulmonic stenosis	—	—
12.	S.J.	F	6	Atrial septal defect; ventricular septal defect; transposition, left superior vena cava to left atrium	—	—
13.	J.B.	F	12	Atrial septal defect and anomalous connection of pulmonary veins	To left superior vena cava	28
14.	E.S.	M	2	Atrial septal defect and anomalous connection of pulmonary veins	To coronary sinus	25
15.	P.L.	F	9	Atrial septal defect and anomalous connection of pulmonary veins	To left superior vena cava	21
16.	V.B.	M	11	Atrial septal defect and anomalous connection of pulmonary veins	To left superior vena cava	43*
17.	V.N.	F	38	Atrial septal defect and anomalous connection of pulmonary veins	To right superior vena cava and right atrium	21
18.	J.H.	F	24	Atrial septal defect, ventricular septal defect (two); pulmonic stenosis and anomalous connection of pulmonary veins	Two right pulmonary veins going to right atrium	28
19.	A.H.	M	17	Atrial septal defect and anomalous connection of pulmonary veins	To right atrium (two from right lung)	28
20.	C.L.	F	3½	Ventricular septal defect and anomalous connection of pulmonary veins	To left superior vena cava	32
21.	J.C.	M	17	Atrial septal defect and total anomalous connection of pulmonary veins	To left superior vena cava	45*
22.	M.J.	M	32	Atrial septal defect and total anomalous connection of pulmonary veins	To left superior vena cava	59*
23.	J.S.W.	M	5/12	Atrial septal defect and total anomalous connection of pulmonary veins	To left superior vena cava	—
24.	J.F.	F	1	Atrial septal defect and total anomalous connection of pulmonary veins	Into coronary sinus (total)	40
25.	D.W.	F	8/12	Atrial septal defect and total anomalous pulmonary venous connection	To coronary sinus	31
26.	A.N.	M	1	Atrial septal defect and ductus arteriosus and total anomalous connection of pulmonary veins	To coronary sinus	—
27.	D.R.	M	2½	Ventricular septal defect and total anomalous pulmonary venous connection	To left superior vena cava	44
28.	L.T.	F	10	Ventricular septal defect	—	30
29.	A.W.	F	9/12	Ventricular septal defect and pulmonic stenosis	—	—
30.	K.G.	F	4	Tetralogy of Fallot	—	42
31.	C.O.	F	11	Ductus arteriosus	—	33
32.	D.F.	F	29	Coarctation of aorta	—	33
33.	L.F.	F	3	Coarctation of aorta	—	34
34.	Y.F.	F	7	Dextrorotation of heart (inferior vena cava on right side)	—	35
35.	E.M.	M	3	Ventricular septal defect	—	42
36.	L.P.	F	42	(Mitral stenosis)	—	—
37.	F.B.	F	29		—	32

* Figure of 8.

cases (Fig. 2), and at times this sign may be misinterpreted unless the possible existence of such an anomaly is considered. Frequently, however, this radiologic feature may not be striking and can be easily overlooked. For this purpose we analyzed the standard roentgenogram taken in the anteroposterior view of 28 of our cases with persistent left superior vena cava as well as an equal number of roentgenograms of normal individuals. The width of the vascular pedicle and the transverse diameter of the chest at the level of the third rib were measured, thereby ex-

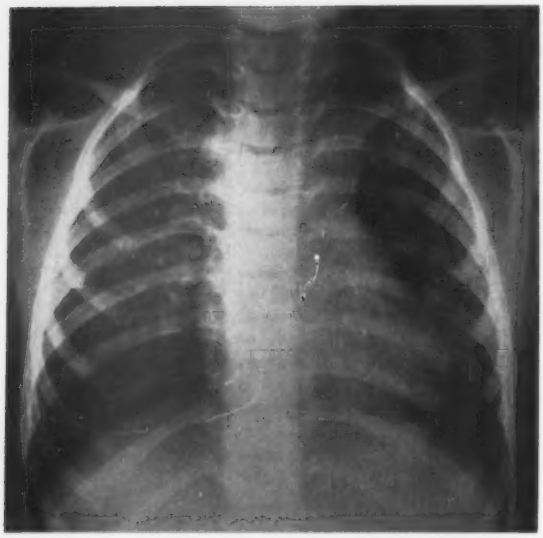


FIG. 2. Standard roentgenogram of the chest in the posteroanterior view, showing the large vascular pedicle.

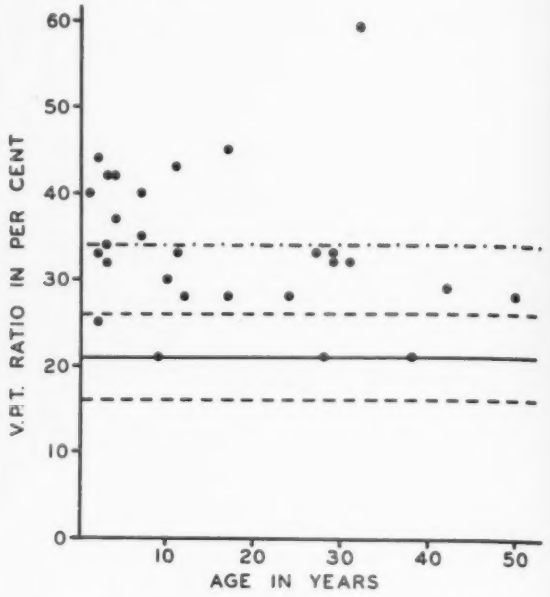


FIG. 3. Scattergram of vascular pedicle–thoracic ratio plotted against age in 28 patients with left superior vena cava compared with mean and 95 per cent confidence limit of the vascular pedicle–thoracic ratio of 28 normal subjects. ——— mean normal VPT ratio; – – – – 95 per cent confidence limit of normal VPT ratio; – • – • – • mean VPT ratio of 28 patients with left superior vena cava.

cluding the shadow of the aortic arch. These figures were then expressed as a percentage according to the equation:

$$\textit{Vascular pedicle–thoracic (VPT) ratio} = \frac{\textit{Width of vascular pedicle}}{\textit{Transverse chest diameter}} \times 100.$$

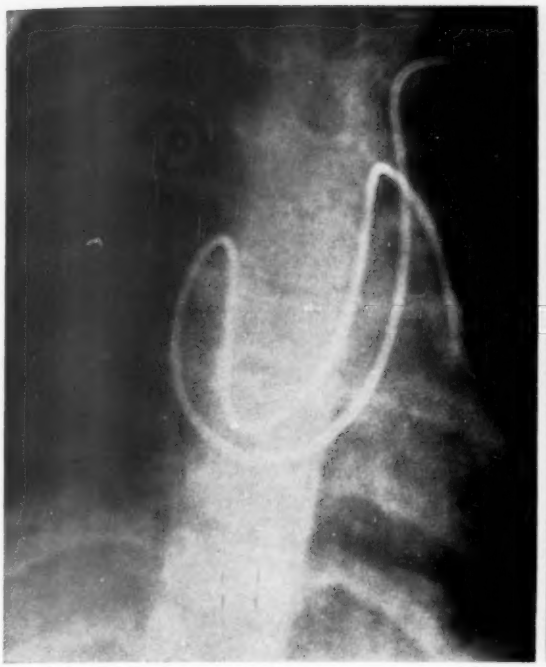
Patients under one year old were excluded from these measurements, because at this age the upper mediastinal shadow is normally large due to the incomplete involution of the thymus gland and therefore the vascular pedicle cannot be accurately measured.

The mean value of the VPT ratio of the 28 controls was 21 per cent (σ = 2.83) whereas that of 28 patients with left superior vena cava was 34 per cent (σ = 8.44). The difference between the means is 13 per cent and the standard error of the difference is 1.7. The difference is statistically significant at $P = 0.01$.

In other words, 86 per cent of the patients with left superior vena cava fall beyond the 95 per cent confidence limits of the normal group, showing that a VPT ratio above 27 per cent can, within these limits, be used as a test to predict deviation from normality and, in all likelihood, the presence of a left superior vena cava (Fig. 3).

CARDIAC CATHETERIZATION

Introduction of the catheter into the venous system of the left arm is more apt to reveal this anomaly. Once the catheter is introduced into the left subclavian vein, the operator may encounter an obstacle at the level of the anastomosis between the left internal jugular and the subclavian veins. This obstacle is overcome, in many instances, with slight manipulation, and the tip of the catheter may then enter the left superior vena cava (Fig. 4). The catheter may meet with a further obstacle a few centimeters below this angle in some cases. In others, however, it may be possible to advance the instrument through the left superior vena cava into the coronary sinus and thereby enter the right atrium (Fig. 3). Whenever this occurs, several blood samples at different points between the right atrium and the subclavian vein should be drawn to rule out the possibility of anomalous connections of pulmonary veins. The left innominate vein is frequently absent in the presence of a persistent left superior vena cava. In our experience it was absent in 16 of the 21 patients in whom the presence of this vessel could be either definitely excluded or confirmed. In a few instances, however, when the left innominate vein is present and patent, it may be possible to withdraw the catheter up to the distal end of the anomalous vessel and advance the instrument through the innominate vein and into the right



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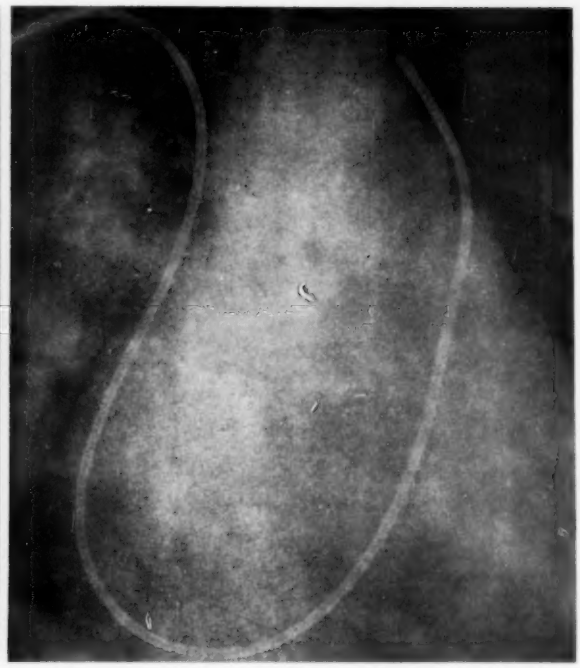

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FIG. 4. Cardiac catheter, introduced through a vein of the left arm, enters the left superior vena cava, coronary sinus, right atrium, right ventricle, main and left pulmonary artery.

FIG. 5. Cardiac catheter, introduced by a right arm vein, enters the right superior vena cava, right atrium, coronary sinus and left superior vena cava.

superior vena cava; the catheter can then follow by the usual route.

The tricuspid valve and the pulmonary valve can only be entered with extreme difficulty when the right atrium has been reached via the left superior vena cava and the coronary sinus (Fig. 4).

In a small group of patients the demonstration of a left superior vena cava may be made in a retrograde fashion. This can occur when the catheter, introduced by the right arm vein, reaches the left superior vena cava via the coronary sinus (Fig. 5), or when the instrument introduced via the left arm vein enters the right atrium via the left innominate vein-right superior vena cava and then, through the coronary sinus, reaches the left superior vena cava (Fig. 6).

Injection of Contrast Medium Through the Catheter: Whenever an obstacle to the passage of the catheter is found we have discovered that it is very useful to observe the anomalous venous pathway with the aid of image amplification and injection of a few cubic centimeters of contrast medium through the catheter.

In two cases we had the opportunity to follow

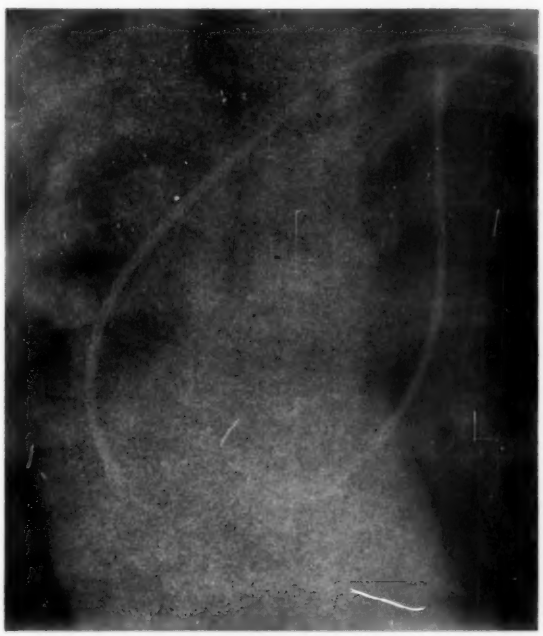


FIG. 6. Cardiac catheter, introduced through a vein of the left arm, enters the left innominate vein, the right superior vena cava, the right atrium, the coronary sinus, and the left superior vena cava.

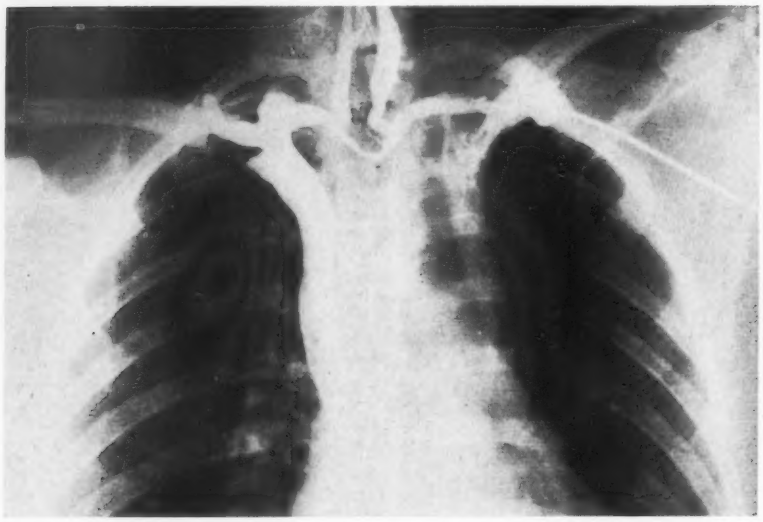


FIG. 7. Contrast medium, injected at the level of the left subclavian vein, outlines the left and right superior venae cavae, as well as a thin anastomotic vessel connecting the venae cavae.

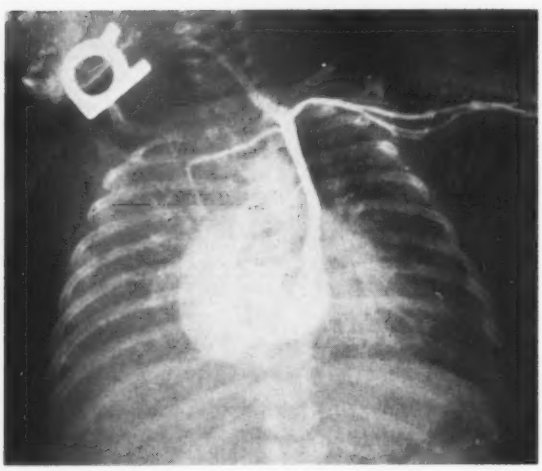
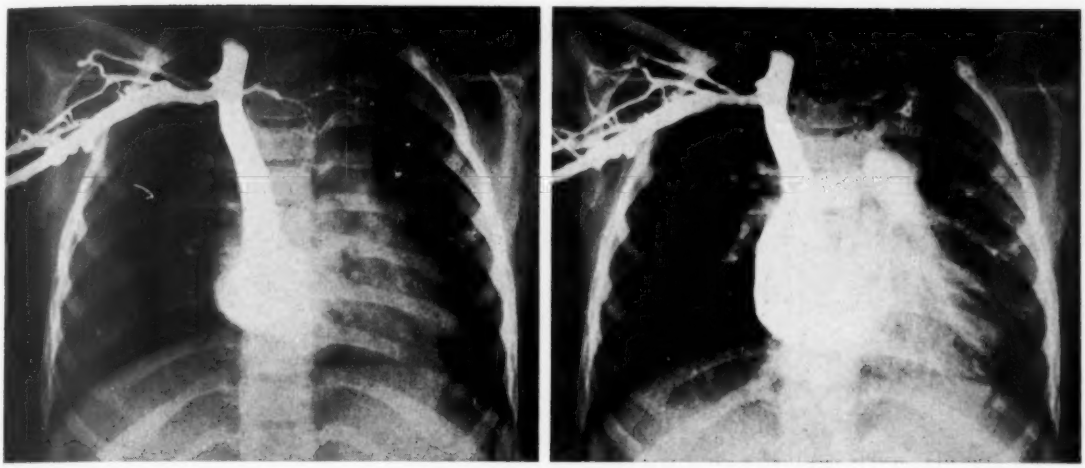


FIG. 8. Contrast medium, injected through a vein of the left arm, outlines the left superior vena cava in its entire length.

this technique, which proved to be very useful in outlining the venous pathway as well as in saving valuable time. The catheter was advanced without difficulty to the junction of the left subclavian and left jugular veins. At this point the instrument could not be advanced any further. The exploring field of our image intensifier was carefully placed over the tip of the catheter, and 2 ml. of 70 per cent Urokon® were injected through the catheter. The flowing of the contrast medium from the tip of the catheter was then observed; it clearly outlined a very thin vessel connecting the left subclavian to the right innominate vein; it also outlined the distal portion of a persistent left superior vena cava (Fig. 7). This demonstrated that further attempts at continuing cardiac catheterization by this route would have been difficult, and indicated that cardiac catheterization via the right arm and angiocardiographic studies should be performed.

Complications During Catheterization: Certain serious, even fatal, complications have been reported following attempts to force the catheter when it will not advance readily. Haeger and co-workers[16] described a case of persistent left superior vena cava associated with Eisenmenger's complex. At the time of cardiac catheterization, performed through the left basilic vein, the tip of the catheter encountered an obstacle at the level of the anastomosis between the subclavian vein and the left internal jugular vein. During vigorous attempts made to overcome the obstacle, a vasovagal syncope occurred and the patient died shortly afterward. At autopsy, a subintimal hemorrhagic lesion was found around the vascular anastomosis and the left vagus.

Peel and associates[17] described a case of left superior vena cava draining into the left atrium associated with patent ductus arteriosus and pulmonary hypertension, with fatal outcome during cardiac catheterization. The authors report that the repeated manipulations of the catheter when it would not freely advance induced a generalized venous spasm of the anomalous vessel and of its tributaries. This prob-



A B

FIG. 9. Contrast medium, injected through a vein of the right arm, outlines the right superior vena cava (A) and partially the left superior vena cava (B) through fine anastomotic vessels.

ably resulted in a sudden decrease in the left ventricular output, with increase in the right-to-left shunt at the ductus level and death because of cerebral hypoxia. These reports stress the hazards of pushing the catheter when there is an obvious obstacle and tend to emphasize the importance of outlining the course of the veins of the superior mediastinum in such cases.

ANGIOGRAPHY

The usefulness of the angiographic examination in cases with persistence of the left superior vena cava is evident. The contrast medium can demonstrate the presence of the anomaly, as well as indicate the pathway, the caliber, and the anatomic relationship of all the venous structures leading to the heart.

The best results are obtained when the contrast medium is injected into the vein of the left arm and the films taken in the anteroposterior position (Fig. 8).

The presence of a left superior vena cava, however, can be demonstrated in many cases even when the injection is performed in the vein of the right arm. There are two helpful signs that should lead the investigator to the correct diagnosis. One of these is a positive sign, encountered in those cases where there is an anastomosis between the two superior venae cavae and the contrast medium outlines the right vessel usually reduced in caliber (Fig. 9A), as well as part of the left superior vena cava (Fig. 9B). A negative sign has been described by Welsh, according to Peel and associates.[17] This consists of a lack of opacification of the left innominate vein while tributaries of the right subclavian vein and right jugular are well outlined by the contrast material.

DISCUSSION

The presence of a persistent left superior vena cava is usually accompanied by other congenital anomalies of the cardiovascular system. This appears evident both from the analysis of our own cases as well as from the data presented in the literature.

It is, however, difficult to establish whether the frequency of such an association is apparent or real, considering that patients without associated lesions are not the subject of investigation. According to Keith and co-workers,[12] the frequency of this anomaly is 1 case in 350 autopsies.

Associated Congenital Anomalies: Persistence of left superior vena cava was associated with other congenital anomalies in 35 of the 37 patients studied by us. The fact that the association of atrial septal defect with anomalous connections of pulmonary veins predominates over any other combination seems interesting.

The association of a left superior vena cava with anomalous connections of pulmonary veins is well understood when the embryologic development is considered. Kjellberg and associates[13] pointed out that if the common pulmonary vein does not develop at all, or develops abnormally, the blood from those parts of the venous plexus that are not drained by this vein continues to empty into the cardinal veins, usually the anterior cardinals. When such a connection between the left pulmonary venous plexus and the

left anterior cardinal veins persists, the continuous flow through this vessel arrests its normal involution.

Whereas in the preceding cases the embryologic correlation is rather evident, we are unable to offer any possible explanation permitting the correlation of persistent left superior vena cava with isolated atrial septal defects. It seems strange, however, that the large number of patients with the combination atrial septal defect-left superior vena cava should be a mere accidental finding.

The discovery of a left superior vena cava during cardiac catheterization or angiocardiography may, therefore, induce the investigator to suspect a possible association with other congenital anomalies and, especially, a left-to-right shunt at the atrial level.

Classification of Types of Left Superior Vena Cava: Numerous classifications of anomalies of the systemic venous return have been proposed by various authors. We believe that the classification which may contribute to the diagnostic evaluation and to the prognosis of the individual case should be made on a functional basis, because the only important fact, once the presence of a left superior vena cava is established, is whether or not a hemodynamic derangement is associated with this anomaly. On this basis we would like to propose the following classification:

1. LSVC with hemodynamic derangement	a. Associated with other congenital anomalies	Atrial septal defect
		Anomalous connections of pulmonary veins, etc.
	b. Anomalous connection of LSVC	LSVC draining into left atrium
2. LSVC without hemodynamic derangement	Isolated LSVC	

Surgical Significance of LSVC: The diagnosis of persistent left superior vena cava associated with other congenital defects has assumed particular importance during the last few years due to the progress of cardiac surgery, especially during open-heart surgery with inflow and outflow occlusion such as at time of hypothermia or extracorporeal circulation. The unsuspected presence of a left superior vena cava may create technical difficulties during these procedures. During extracorporeal circulation, according to Cooley and associates,[18] the presence of a left superior vena cava deserves special consideration because if it is not discovered before perfusion is begun, the results may be disastrous. These authors suggest that the left superior vena cava should be occluded inside the pericardium so that venous return from the hemiazygos vein can also be controlled during cardiopulmonary bypass.

Our experience is based upon several cases in which, during open-heart surgery performed with the aid of hypothermia and circulatory occlusion, the difficulty presented by the presence of a left superior vena cava was obviated through the occlusion of the coronary sinus. This was made possible by the fact that the surgeon, with the benefit of an accurate preoperative diagnosis, had prepared a special catheter with a latex balloon at its tip. The flow from the left superior vena cava was thus arrested by the introduction of the catheter into the coronary sinus and insufflation of the balloon in situ.

Summary

On the basis of our cases as well as the data in the literature we can conclude that discovery of a left superior vena cava during cardiac catheterization or angiocardiography is of great importance both from the clinical and surgical standpoint. It is clinically important because it indicates the probable association with other congenital anomalies and especially with a left-to-right shunt at the atrial level, and surgically important because it indicates, prior to operation, certain technical procedures which will be necessary to prevent disastrous complications at time of cardiac surgery.

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New Methods

Newer Technics Helpful in the Study of Regurgitant Lesions of the Cardiac Valves*

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IN THE PAST decade newer methods and instruments of examination have improved the accuracy of cardiac diagnosis. However, a number of lesions and their resultant physiological impact continue to impose a considerable task in terms of definitive recognition and precise quantitation. Outstanding among these are the valvular insufficiencies.

The present communication considers the value of two radiologic technics, cardiac ventriculography and suprasternal thoracic aortography, which have been utilized in an effort to improve our ability to estimate regurgitant volumes. The discussion includes a brief description of both procedures, as well as a consideration of their use in the study of valvular insufficiencies.

Both radiologic methods have in common the requirement of a direct needle puncture of a cardiac chamber or great vessel and the rapid injection of a radiopaque substance, with rapid serial filming.

CARDIAC VENTRICULOGRAPHY

The procedure, as described by Lehman, Musser and Lykens,[1] involves the direct transthoracic needle puncture opacification of a cardiac ventricle. It is performed by a thoracic surgeon, a cardiologist and a radiologist working together as a team.

The patient is positioned for horizontal right lateral projection when left ventricular opacification is performed, and in a horizontal anteroposterior projection for right ventricular study. A special 6 inch, moderate bevelled needle with single side hole and closed end is inserted directly into the ventricle via a subxiphoid approach, under manometric control and with constant electrocardiographic monitoring.

The direction of the needle pass is estimated by considering the size and configuration of the heart from a study of a preliminary film taken with lead numerals taped over the chest in the area of roentgen projection of the ventricle.

The needle is inserted swiftly. When satisfactory positioning of the needle tip has been obtained, as determined by observation of the pressure wave monitoring, the contrast material is rapidly injected into the ventricular cavity by means of a pressure injector. Rapid serial filming is obtained throughout the period of injection and for a short time thereafter.

In the presence of a valvular insufficiency, regurgitant opacification of the associated atrial chamber is observed (Fig. 1). This is graded 0 to 4 plus, depending upon the intensity of reflux opacification of the atrium. With a competent valve, no significant reflux across the atrioventricular valve is observed.

INDICATIONS

Quantitation of Regurgitation at the Atrioventricular Valves: Rheumatic mitral stenosis is frequently accompanied by a variable degree of mitral regurgitation. In view of current surgical accomplishments,[2] it becomes imperative to determine preoperatively whether or not the regurgitation is dynamic. When insufficiency is a solitary

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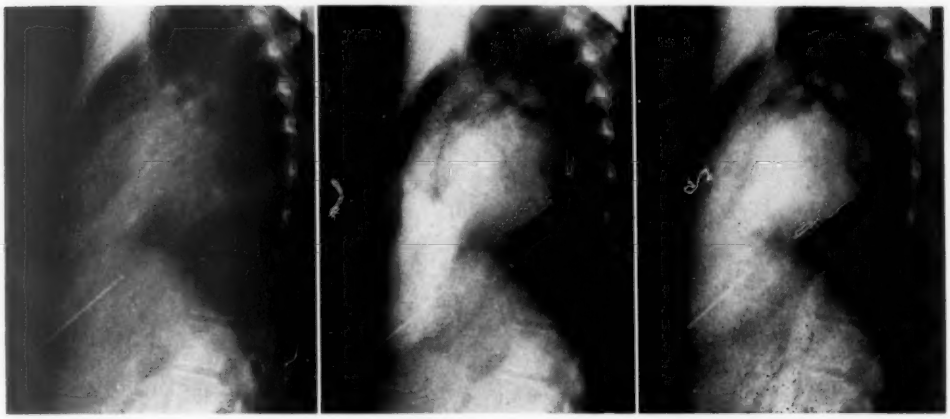
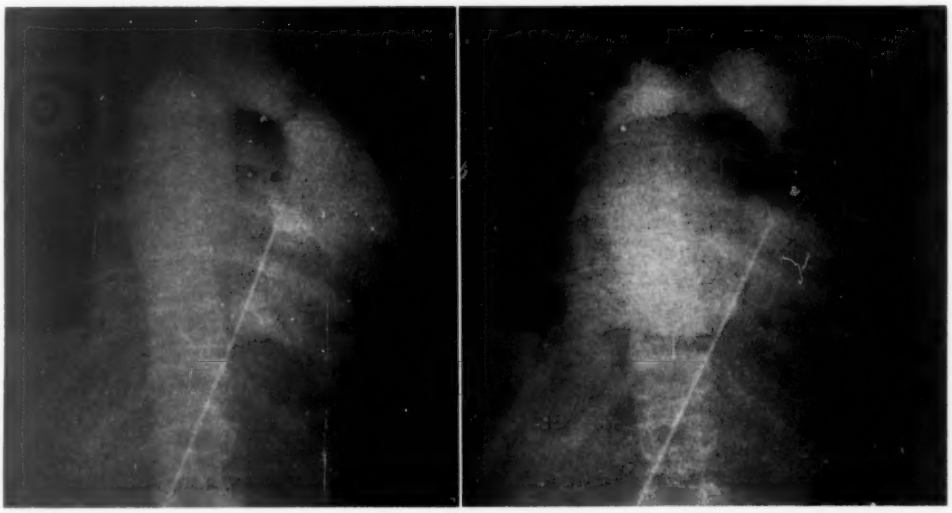


A B C

FIG. 1. Cardiac ventriculography (left). Case B. B. Marked mitral insufficiency. A, film taken one-half second before injection of dye into left ventricle. B, film at one and a half seconds. Note marked regurgitant opacification of the left atrium. C, left atrium opacified at three seconds.



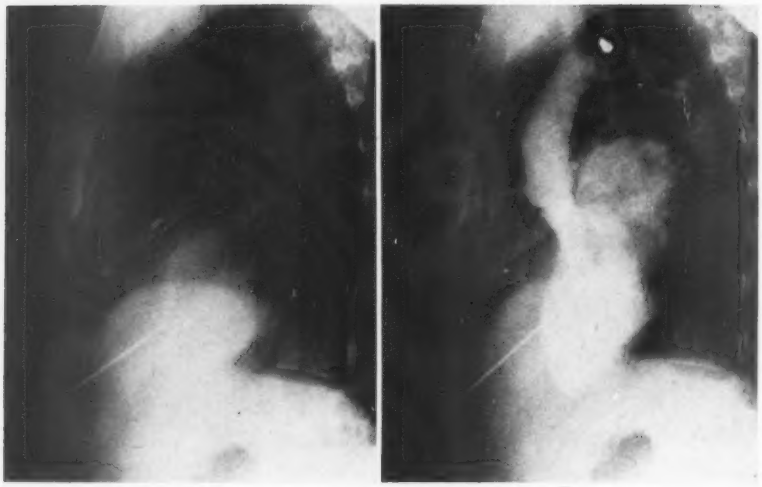
A B

FIG. 2. Cardiac ventriculography (right). Case V. G. Tricuspid regurgitation. Injection of contrast material into right ventricle (A) results in immediate opacification of right atrium (B), confirming presence of tricuspid regurgitation. Left ventriculography was negative.

lesion, clinical evaluation is reasonably accurate. However, with combined mitral stenosis and insufficiency, the clinical estimation of mitral insufficiency becomes more difficult. It is under such circumstances that cardiac ventriculography is particularly helpful.

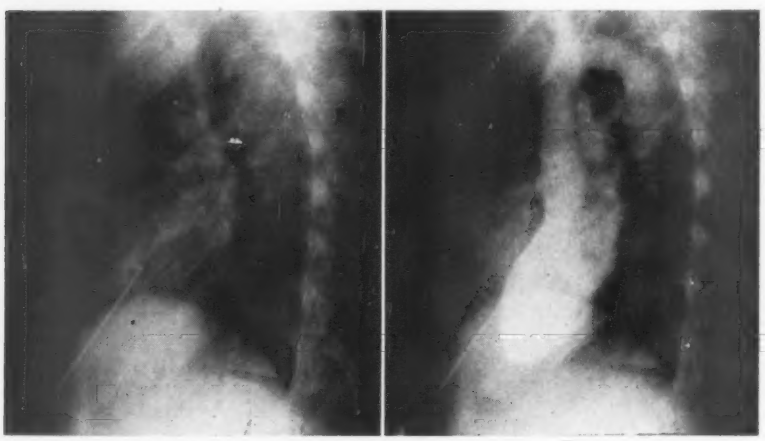
There are two other clinical problems in which needle puncture opacification of the ventricular chambers is valuable. One involves the diagnosis of mitral regurgitation in the presence of rheumatic aortic valve disease. The rough murmur of aortic stenosis may be transmitted to the apex and suggest the presence of mitral regurgitation. The other concerns the syndrome of tricuspid regurgitation which often masquerades as mitral regurgitation in patients with pure mitral stenosis.[3] In either case, cardiac ventriculography (left) would be negative, while in the latter situation, cardiac ventriculography (right) would be positive (Fig. 2).

A previous study has demonstrated that grade 2 to 4 reflux opacification of the atrium on cardiac ventriculography always indicated dynamic valvular leak.[4] A grade 1 reflux opacification of the atrium may occur in the presence of major mitral stenosis if a large enough central aperture



A B

FIG. 3. Cardiac ventriculography (left). Case B. N. Traumatic mitral regurgitation following mitral commissurotomy. A, before injection. B, after injection of dye into left ventricle. Note marked regurgitant opacification of left atrium.



A B

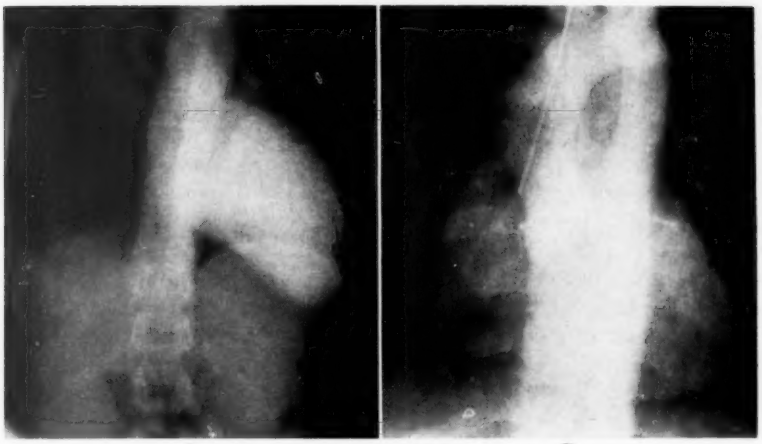
FIG. 4. Cardiac ventriculography (left). Case G. R. Atrial septal defect (secundum type) associated with mitral regurgitation. A, before injection. The demonstration of reflux opacification of left atrium (B) points to need of surgical correction of the mitral regurgitation.

is present between the fused commissures. In pure valvular stenosis, the radiopaque material does not pass into the atrial chamber.

Evaluation of Surgical Procedures: Cardiac ventriculography has been most helpful in assessing the results of the modern methods for correction of rheumatic mitral regurgitation. A decrease in reflux opacification of the left atrium postoperatively has invariably been accompanied by a diminution in the clinical manifestations of the disease. In our experience, it is preferable to those methods which rely on the analysis of left atrial pressure pulse curves.[5]

Direct needle puncture opacification of the left ventricle has been employed in isolating the cause for a poor clinical response to a previously performed mitral commissurotomy. When a large quantity of contrast material passes in retrograde fashion from left ventricle to left atrium, categoric proof is obtained of traumatic mitral regurgitation, which may have developed as the result of a tear of the leaflets, their supports or of the annulus (Fig. 3).

Congenital Heart Disease: Cardiac ventriculography is useful in demonstrating the regurgitation at either the mitral or tricuspid valve that commonly accompanies defects in the area of the atrioventricular canal. Although this finding



A B

FIG. 5. Suprasternal thoracic aortography. Case E. A. Aortic regurgitation. A, marked reflux opacification of left ventricle following injection of dye into the ascending aorta indicates presence of aortic regurgitation. B, following open heart surgery, aortography reveals no aortic valve incompetence.

can no longer be accepted as diagnostic of an atrial septal defect of the ostium primum type,[6] as opposed to a secundum defect, it points out the need for surgical correction of the valvular insufficiency at the time the septal lesion is repaired (Fig. 4).

COMPLICATIONS

The minor reactions to cardiac ventriculography include non-specific chest pain, a sensation of warmth and flushing, palpitation, headache and nausea. They are all transient.

The major complications include arrhythmias, hypotension, intramyocardium injection of dye and conduction defects.

Cardiac ventriculography is a procedure not devoid of real hazard. The greatest danger lies in the inadvertent intramyocardial injection of the radiopaque medium. In our series of over 280 consecutive cases there have been three deaths due to intramyocardial injection. One patient died immediately after the procedure. The second patient died in a state of shock seven hours after the procedure. Intramyocardial injection produced complete heart block in a third patient, with death occurring six months later during a Stokes-Adams attack.

The procedure is not applicable to infants or young children.

Suprasternal Thoracic Aortography

This procedure involves the direct needle puncture opacification of the ascending aorta, as described by Lehman, Lemmon, Boyer and Fitch,[7] performed as in cardiac ventriculography by an experienced team.

The patient is positioned over the serial filming device, with head and neck hyperextended and rotated toward the right, exposing the suprasternal notch. The needle is inserted in the midline, slightly above this notch. The direction and depth of needle insertion is determined from study of preliminary films. The needle pass is made under electrocardiographic control and manometric monitoring. Once needle penetration of the ascending aorta is accomplished, the needle tip is then advanced down the lumen of the ascending aorta to position its tip slightly above the level of the aortic sinuses. The radiopaque substance is injected by a pressure injector in no more than three seconds. Rapid serial filming is begun a half second prior to the injection to secure a control film, and is continued throughout injection and for a short time thereafter. Immediately upon completion of the injection, the needle is withdrawn.

INDICATIONS

Aortic Regurgitation: Suprasternal thoracic aortography provides a means of quantitating aortic regurgitant lesions (Fig. 5). The technic obviates reliance upon crude methods, such as the use of the pulse pressure or the character and force of the peripheral arterial pulses.

It is of value in assessing the magnitude of regurgitation in patients with combined lesions of the aortic valve. If dynamic aortic regurgitation is an issue, performance of an isolated aortic commissurotomy would be of little value.

Another important application of the study concerns the nature of the early diastolic murmur along the left sternal border in patients with

rheumatic mitral valve disease. The detection of aortic regurgitation by suprasternal thoracic aortography may seriously influence the desirability of performance of a mitral commissurotomy.[8]

Evaluation of Surgical Procedures: Contemplating the future development of surgical technics for the correction of aortic regurgitation, it would appear that pre- and postoperative comparison of the amount of reflux of radiopaque dye from the aorta into the left ventricle would serve as an objective method of evaluating the success of these procedures. Figure 5B illustrates the effectiveness of open heart technic for the correction of aortic regurgitation in which bicuspidization of the incompetent aortic valve was accomplished surgically.

Aortography may also be used to assess the degree of aortic valve leak which may follow an unsuccessful aortic commissurotomy.

COMPLICATIONS

Retrosternal pain commonly develops after suprasternal thoracic aortography, probably due in large measure to needle trauma and to varying degrees of superior mediastinal bleeding or hematoma. The gravest danger is needle trauma tear of the aortic wall and aortic hemorrhage. In the initial series of ninety-three consecutive patients who had been subjected to this procedure at the time this article was submitted for publication, there had been no serious morbidity or any mortality. However, in an additional series of fifty-three suprasternal thoracic aortographies, there has been one fatality due to aortic bleeding at the site of needle laceration of the aortic wall. This fatality has been reported in detail as an Addendum to the publication of Lehman et al.[7]

The hazard of aortic bleeding has placed limitations on our application of this procedure, and we are now utilizing it only in selected cases with a prominent ascending aorta, and are giving preference to a catheter thoracic aortographic type of procedure for evaluation of aortic insufficiency. Certainly the procedure of suprasternal thoracic aortography does not appear to be applicable to infants and young children.

COMMENT

There has been a definite need for radiologic procedures which permit assessment of cardiac valvular insufficiencies. The inadequacies of clinical evaluation and quantitation of valvular leak, particularly in the presence of combined stenotic and regurgitant lesions of cardiac valves, have emphasized the desirability of an objective assessment of valvular insufficiencies.

It is beyond the scope of this paper to more than mention the poor correlation existing between the intensity of a cardiac murmur and its physiologic significance. This also applies to electrocardiographic patterns and, in some cases, to size of the heart.

The methods described in this communication have, in our hands, been useful diagnostic aids and important adjuncts in the study of regurgitant lesions of the cardiac valves.

SUMMARY

The usefulness of two new radiologic technics, namely, cardiac ventriculography and suprasternal thoracic aortography, in assessment and quantitation of cardiac valvular regurgitant lesions is discussed.

Direct needle puncture opacification of the ventricular chambers and the ascending aorta permits an objective appraisal of degrees of regurgitation of the mitral, tricuspid and aortic valves.

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Historical Milestones

Description of Congenital Pulmonary Atresia and Tricuspid Stenosis (Delmas, 1826)

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CONGENITAL cardiac abnormalities resulting in a non-functioning right ventricle are considered as a group in Taussig's[1] classic book on congenital heart disease, including tricuspid atresia with ventricular septal defect and pulmonary atresia with tricuspid stenosis. It is postulated that right ventricular hypoplasia, independently of the mechanism of its production, produces similar hemodynamic alterations and clinical findings.

Some discrepancies, however, were found in the electrocardiographic and radiologic findings of tricuspid atresia, in which left axis deviation in the frontal plane is almost always present, from those of pulmonary atresia and tricuspid stenosis, showing a normal ÂQRS or even right ventricular hypertrophy. Novelo et al.[2] were the first to remark on the differences in the abnormal development of both conditions. They postulated that in that second group, the late production of pulmonary atresia prevented the formation of an interventricular defect. The resistance to right ventricular outflow initially leads to concentric hypertrophy, and later, through a hemodynamic mechanism, to tricuspid stenosis. They suggested a distinction of both anatomic types of non-functioning right ventricle: those with hypoplasia of the inflow tract and normal or absent outflow tract, which show left axis deviation, and those with hypertrophy of the inflow tract and potential, or actual, right ventricular hypertrophy.

Chiche, in 1952,[3] remarked on the contrast between tricuspid atresia with right ventricular hypoplasia on the one hand, and small but patent tricuspid orifice with underdeveloped right ventricular cavity, but with normal or even hypertrophied walls, on the other. He postulated that the last group of cases, corresponding to tricuspid stenosis, do not belong to, and must be distinguished from, tricuspid atresia.

Durand and Metianu,[4] however, include these cases under the heading "tricuspid atresia or hypoplasia." They consider congenital tricuspid stenosis as an anatomic variation, with similar hemodynamic abnormalities as tricuspid atresia with intact ventricular septum. In both instances, a defect of the atrial septum and a patent ductus arteriosus assure the blood flow to the lungs, and a considerable right-to-left shunt at the atrial level is present. They emphasize the rarity of tricuspid stenosis. The same authors, in the historic introduction, indicate that the first descriptions of tricuspid atresia belong to Hunter (1784), Kreisig (1814–1817) and Holmes (1824). Thereafter, the cases of Valeix (1834), Vrolik (1849) and Peackock (1853) are cited.

An article published by M. Delmas in 1826 has been found in which a case of congenital tricuspid stenosis with pulmonary atresia and right ventricular hypoplasia is reported in detail, with a brilliant interpretation of the circulatory disorders imposed by the anomaly, and a brief review of the literature up to that date. It is the purpose of this paper to present the following translation of that report[5] which was published in a journal entitled *Éphémérides Médicales de Montpellier* (*Figs. 1 and 2*).

* * *

On May 24, 1822, Mrs. A., at the term of her fifth pregnancy, delivered after two hours of labor. The baby was female, of an ordinary volume and well formed in appearance. She was still and in an apoplectic state. I performed the section of the umbilical cord, leaving the blood to flow during a few moments. The baby recovered the sense, and began to breathe

ÉPHÉMÉRIDES

MÉDICALES

DE MONTPELLIER.

TOME I.

A MONTPELLIER,

CHEZ GABON et Comp°, Libraires, Grand'Rue;

ET A PARIS,

CHEZ LES MÊMES LIBRAIRES, Rue de l'École de Médecine;

1826.

FIG. 1. Frontispiece of the journal, *Éphémérides Médicales de Montpellier*, in which Delmas' original description of congenital pulmonary atresia with tricuspid stenosis is contained, and herewith reproduced.

and cry. A universal blueness remained, especially marked in the face, and notably on the upper eyelids. Respiration remained somewhat rapid, especially while the baby was awake. On the other hand, the slightest effort or the smallest agitation accelerated the respiration, and made it difficult, or even transiently stopped it. The skin then had a livid hue, and suffocation was impending. Perfect rest was also necessary, so that she could be breast fed. By means of these cares, the difficulty in taking the breast diminished in part, the nutritional functions took great activity, and she gained considerable weight. Meantime, frequent colic reproduced respiratory

(64)

OBSERVATION *sur une Cyanopathie, ou maladie bleue, dépendant d'une affection organique du cœur; par* M. Delmas.

Le 24 mai 1822, M^me^ A***, parvenue au terme d'une cinquième grossesse, accoucha après

(65)

deux heures de souffrance. L'enfant était du sexe féminin, d'un volume ordinaire et bien conformé en apparence; il était roide, immobile et dans un état apoplectique. Je fis la section du cordon ombilical et laissai le sang s'écouler pendant quelques instans: la petite fille reprit alors ses sens et commença à respirer et

FIG. 2. Title and first paragraphs of the paper published by M. Delmas in 1826.

trouble, anxiety and suffocation. A more violent attack led suddenly to death two and a half months after birth. Without any doubt, after the previously mentioned symptoms of the existence of some organic anomaly of the heart, I obtained from the parents permission to open the body. Professor Broussonnet, who attended the little patient during life, was present at the autopsy.

AUTOPSY

All the body surface offered a violet color, more marked in the superior parts. The capillary system was generally engorged with black blood. The tongue was tumefied and dark, protruding out of the mouth.

The skin of the skull, incised to open this bony structure, oozed a great quantity of blood that came from the surface of the bones. These had a bluish hue, due to the bloody engorgement of their diploë.

The meningeal vessels were markedly infected; those of the brain were no less infected and a number of droplets appeared on the incision made into the substance of this organ, which was otherwise healthy.

The lungs were poorly colored, except on their posterior aspect. The abdominal organs did not show anything remarkable.

The heart (Fig. 3) was more rounded at the apex, and smaller in volume than in the normal subject. The atria were distended by the blood, especially the right atrium, which was two times as large as the left; this last offered an appendix prolonged just to the corresponding ventricle. This left ventricle seemed to constitute three-fourths of the heart's volume. The right ventricle appeared atrophied, as did the pulmonary artery, which only had a third of the aorta's dimensions. It gave two branches of greater

size than the trunk (pulmonary branches), but smaller than in a healthy subject. Its prolongation (ductus arteriosus) was even larger, and was united with the aorta in the ordinary fashion.

There only existed a single venous trunk for the right lung.

Examination of the interior parts of the organ confirmed what the external aspect had already led one to presume that the right ventricle was obliterated and the pulmonary artery obstructed; the latter was closed at its origin by the mutual adhesion of the semilunar valves. The former (right ventricle) had the same thickness of the wall as in the normal state, but its cavity was reduced to a kind of narrow channel, of two and a half lines long (5 mm.), with uneven and close walls that could hardly contain a pin. The atrioventricular orifice was replaced by a small oval opening whose longest diameter (anteroposterior) measured one and a half lines (3 mm.), and the shortest only one line (2 mm.); it was, in other words, hidden in the fleshy columns of the right atrium.

The right atrium itself, apart from its great volume, showed some peculiarities: (1) the absence of the Eustachian valve; and (2) the persistence of the foramen ovale, where the valve, quite thin and short, left an opening 6 mm. long.

Concerning the left heart chambers, they were in the most natural state, except for the opening of the pulmonary veins, of three in number only, in place of four as in the normal state.

It is easy to judge how such a disposition could produce circulatory and respiratory disturbance. This is what we are going to emphasize, taking a view on the course of the circulation, first, during intrauterine life, second, after birth.

Intrauterine Circulation: The blood which arrived at the right atrium through the superior vena cava, instead of passing to the right ventricle, pulmonary artery, ductus arteriosus and descending aorta, was mixed with that of the inferior vena cava, and passed with it through the foramen ovale to the left atrium and ventricle, and then to the ascending aorta. This artery conducted the blood not only to the superior parts, but, as in the adult, also to the inferior. A small portion refluxed into the ductus arteriosus and was carried to the lungs. This type of circulation could be present without much trouble to the fetus; only the superior parts of the body receiving less pure blood than in the normal state; from it undoubtedly was derived the livid hue of the face, which was already apparent at birth.

Extrauterine Circulation: Venous blood, instead of flowing entirely through the right ventricle and pulmonary artery, passed, as before birth, to the left chambers and into the aorta; this dark blood mixed with the red blood carried by the pulmonary veins. A portion of this mixed blood, refluxing through the ductus arteriosus, went to the lungs to be vitalized, and returned through the pulmonary veins to be mixed again. Undoubtedly, the pulmonary vessels were partially developed after birth; this is the sole change produced in the circulatory system.

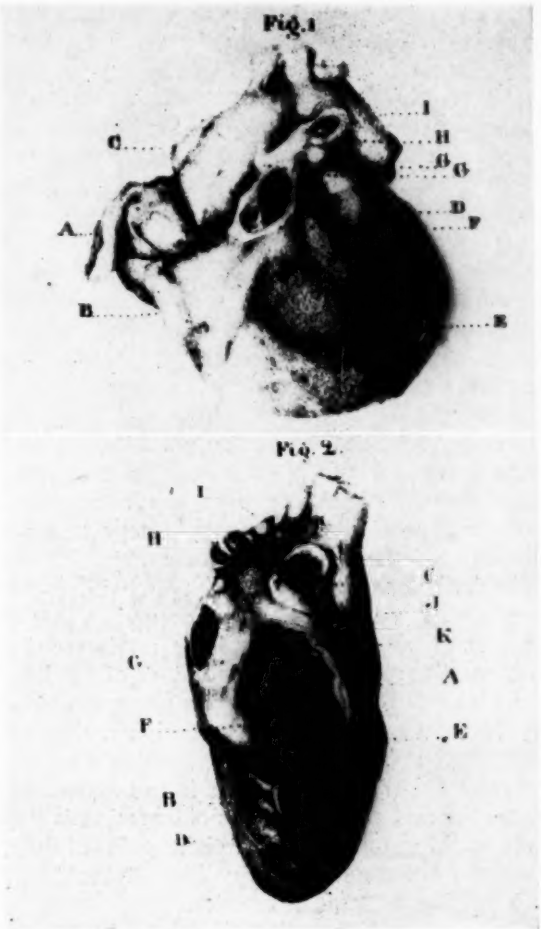

FIG. 3. Original Figures 1 and 2, reproduced from the article of Delmas. Their legends are as follows: Fig. 1. A, right auricle, opened through its superior part. B, right ventricle. C, superior vena cava. D, left auricle. E, left ventricle. F, pulmonary artery, opened to show the fused semilunar valves. G and G′, left and right pulmonary artery. H, ductus arteriosus, opened to show its communication with the aorta. J, aortic arch (heart viewed anteriorly).

Fig. 2. A, right auricle, extensively opened. B, right ventricle. C, superior vena cava. D, right-inferior aspect of the left ventricle. E, right ventricular opening. F, coronary vein. G, inferior vena cava. H and I, right and left pulmonary veins. J, aortic arch. K, patent foramen ovale (heart viewed from its right side).

From this disposition two different effects resulted: (1) all parts of the body received, in place of arterial blood, a mixture of dark and red blood: from that resulted the blue color of the skin; and (2) the lungs could act but on this same mixture; their work was half done, respiration, therefore, becoming more frequent than in the normal state. On the other hand, they were dependent on the aortic system, which could easily transmit to them the disturbance produced by the slightest agitation; from it came dyspnea and suffocation.

This organic disposition lies between that of chelonic reptiles, which have two atria and one ventricle, but where the pulmonary artery has a distinct origin from that of the aorta, and frogs, which have only one atrium and one ventricle, the pulmonary artery being a branch of the aorta. In these animals, respiration, dependent somewhat on will, is not exposed to the disturbances occurring in this infant. This parallel furnishes an interesting observation: the body temperature of our little patient was not below that of a normal subject. It is not to this type of circulation and blood vitalization, therefore, that the feeble temperature of cold-blooded animals is to be ascribed. Another and no less curious observation is that the child's growth and weight gain did not suffer from the venous qualities of the blood circulating through its arteries.

The anomaly just described is a rather rare cause of cyanopathy, although, according to Meckel, it is less rare than transposition of both pulmonary artery and aorta. Senac vaguely says (volume 1, page 179) that the right ventricle was sometimes absent. His work will always be valuable for anatomy and physiology, but the pathologic part is already old. The value of precise and positive observations is not appreciated, and we must arrive at a more modern epoch to find detailed examples of the present deformity. Baillie (*Anat. Pathol.*, page 30) reports a case completely similar to ours, that was observed by Hunter: obliteration of the pulmonary artery, right ventricular atrophy, enlargement of the right atrium, patent foramen ovale and ductus arteriosus, blue color of the skin and difficult respiration. Those are the points of resemblance which unite this case to that of M. Delmas. The infant lived only thirteen days.

The paper of Meckel on congenital anomalies of the heart (*Journ. Complém.*, May 1819) contains many observations of the same type, and several almost identical. Also, (1) in the observation of Farre and Weston, the pulmonary artery was well obliterated, but the right ventricle existed, and a perforation of the ventricular septum permitted the passage of blood from one chamber to the other, and into the aorta, which overrode both ventricles. This occurred also in the infant examined by Howship. (2) The cases observed by Farre and Hodgson offer the following features in common with our observation: the pulmonary artery was obliterated, the foramen ovale and ductus arteriosus were patent and large and the right ventricle was atrophied. In all these infants respiratory disturbances and blue skin were present. All died prematurely (at most six months) after birth, and almost all were females. The temperature was diminished in some, but in others, as in our case, it was normal. Their growth was not retarded by this anomalous disposition of the circulatory system, and we can make the same remark on the majority of subjects with cyanopathy of whatever cause: this suggests that arterial blood is less necessary to nutrition than to stimulation of the different organs. In effect, in the majority of these patients, we observe a kind of torpidness, of apathy, which could well be attributed to the need of being in the most complete rest, to avoid the anxieties that could reproduce every agitation.

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Diagnostic Shelf

Myocardial Infarction Pattern Disclosed by Ventricular Extrasystoles

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EXTRASYSTOLES associated with myocardial infarction do not as a rule differ from extrasystoles encountered in other disorders. Rarely, however, extrasystoles arising in the presence of myocardial infarction may have a distinctive appearance. Diagnostic changes resulting from a myocardial infarction have been observed in atrial, nodal and ventricular extrasystoles.[1–3]

Dressler[1] described a case of myocardial infarction masked by bundle branch block but revealed by occasional premature ventricular systoles. Since left bundle branch block notoriously hides the electrocardiographic signs of myocardial infarction, extrasystoles must be examined diligently in the tracings taken from such patients. These extrasystoles, if present, may be the only clue to the diagnosis of infarction.

Scherf and Schott[2] reproduced an electrocardiogram of a patient suffering from a recent myocardial infarction which demonstrated diagnostic abnormalities in atrial extrasystoles. These consisted of changes in the final deflection of the QRS complex with a high take-off and a dome-shaped segment. These changes were thought to be due to the Ta wave of the premature inverted P wave.

Simonson, Enzer and Goodman[3] reported an example of ectopic nodal beats unmasking a pattern of myocardial infarction or coronary insufficiency in the presence of intraventricular block.

We present in this communication an example of abnormal ventricular extrasystoles in a patient who previously suffered from myocardial infarction and left ventricular hypertrophy. Although the final electrocardiogram revealed abnormalities it was not specifically diagnostic of infarction. The ventricular extrasystoles, however, were sufficiently altered in several of the leads, particularly in the right precordial leads, to uncover a pattern of a previous myocardial infarction.

CASE REPORT

The patient was a sixty-nine year old white man who suffered from arterial hypertension of many years' duration. On August 24, 1958 he was seized suddenly with severe substernal chest pain and an electrocardiogram was immediately recorded (Fig. 1A). The patient was followed-up in the hospital; the clinical course was typical of a recent myocardial infarction. His oral temperature was slightly elevated for a few days during the first week of his illness. The serum glutamic oxalacetic transaminase activity (SGOT) reached a peak of 90 units in twenty-four hours. The blood pressure averaged 145/90 mm. Hg. He was not in heart failure. A roentgenogram of the chest showed left ventricular enlargement. He was treated with conventional and anticoagulant drugs. An electrocardiogram taken on September 1, 1958, one week after admission (Fig. 1B), showed the serial changes typical of a recent anterolateral myocardial infarction. In addition, there were T wave changes of left ventricular ischemia.

The patient made a good recovery. A follow-up electrocardiogram taken on December 1, 1958, three months after his hospital admission, demonstrated frequent ventricular extrasystoles (Fig. 1C). More important, the pattern of myocardial infarction was not clearly demonstrated in the normal sinus beats. However, the ventricular premature systoles in leads V_1, V_2, V_3 and aVR now showed a deep Q wave, changes in the RS-T segment, and a deeply inverted T wave.

COMMENTS

When a myocardial infarction heals specific changes in the electrocardiogram are not always

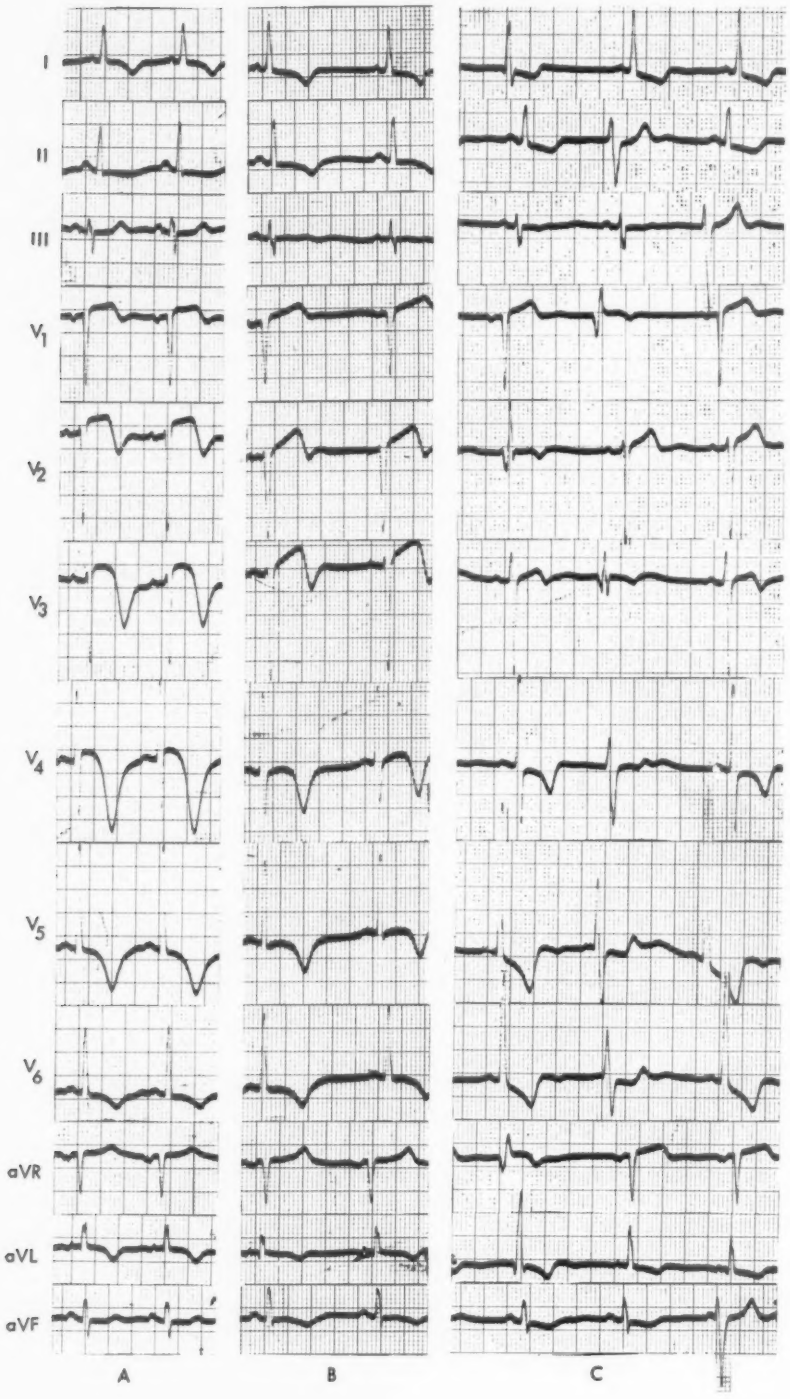

FIG. 1. Serial electrocardiographic study. A, record of August 24, 1958, taken on admission to the hospital when patient experienced chest pain. B, record of September 1, 1958, showing serial changes of acute anterolateral wall infarction. C, record of December 1, 1958, after recovery, shows ventricular extrasystoles. Note the Q wave and inverted T wave of these extrasystoles in leads V_1, V_2, V_3 and aVR. See text.

present. There are many documented instances of myocardial infarction in which electrocardiographic changes are either minimal or limited to the T wave. Ordinarily the electrocardiographic diagnosis of an old infarct is established with confidence only when there are unmistakable fixed changes in the QRS complex. The clinical course, as well as the electrocardiographic records, leave no doubt that our patient suffered a myocardial infarction. When the patient recovered the QRS complexes in the normal sinus beats were not diagnostic. However, abnormal Q waves, as well as RS-T segment changes and inversion of T waves, were clearly noted in the extrasystoles of the follow-up tracing.

In interpreting electrocardiograms it is axiomatic not to overlook any ectopic beat. Unfortunately our present method of assembling electrocardiographic tracings on charts is handicapped by a rigid conformity and a lack of space. Too often when a tracing is mounted the technician omits an extrasystole because the space allotted for a particular lead is inadequate. In recent months two papers have appeared in which the importance of examining isolated extrasystoles in confirming the diagnosis of an infarction is discussed.[4,5]

Summary

Extrasystoles may be an important clue to the diagnosis of a myocardial infarction. In atypical electrocardiograms, particularly in patients with an intraventricular block, abnormalities of ectopic beats may be extremely helpful in confirming the diagnosis of a myocardial infarction. A serial electrocardiographic study of a patient with hypertension who experienced a myocardial infarction is presented in which the pattern of an infarction was later uncovered by changes in the ventricular extrasystoles.

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Progress Notes in Cardiology

Edited by EMANUEL GOLDBERGER, M.D., F.A.C.C.
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The Electrocardiogram During Open Heart Surgery

AN INTERESTING study of the electrocardiogram during open heart surgery with a heart lung machine has been described by Drs. Leonard M. Linde, Eva M. Kavan and James V. Maloney (Department of Pediatrics, Anesthesiology, and Surgery, School of Medicine, University of California, Los Angeles). In this study, the electrocardiogram was continuously monitored and recorded in twenty-five consecutive patients placed on a pump-oxygenator of the Gibbon type. A single bipolar lead was recorded similar to lead I of the standard electrocardiogram with electrodes on each scapular area. Recording was on a Grass 8 channel electroencephalograph machine with various paper speeds. While the main deflections, such as the P wave, QRS complex, T wave, cardiac rate, and general electrocardiographic configurations could be recognized, this single tracing did not permit accurate measurements of the various intervals such as the P-R, QT and QRS.

Ventricular septal defect was the most frequent anomaly while other diagnoses included tetralogy of Fallot, transposition of the great vessels, aortic stenosis and mitral regurgitation. Most of these early cases were relatively poor risk patients. In these twenty-five patients, the effects of various aspects of the procedure, and prognostic and diagnostic significance of certain electrocardiographic changes were noted.

Table I indicates the phases of the operation which were most frequently associated with cardiographic abnormalities. In Table II, the usual abnormalities are outlined.

Premature ventricular contractions, by far the most frequent arrhythmia, were noted in twenty-one of the twenty-five patients when the chest was opened, with introduction of large retractors and with rib manipulation. In several patients, transient ventricular fibrillation was recorded during these manipulations. In seven patients, flattening and disappearance of the P wave, changes in the P-R interval and even atrioventricular dissociation were noted. Pericardial incision also produced ectopic beats and variation in the T wave. In all twenty-five patients, palpation of the heart and insertion of a needle for intraventricular blood sampling produced marked changes including long runs of ventricular ectopic beats, runs of ventricular tachycardia and even short episodes of ventricular fibrillation. Atrial manipulation with insertion of the venous cannulae produced premature ventricular contractions and various degrees of heart block in ten patients. In two patients with transposition of the great vessels, coronary artery dissection produced grossly abnormal electrocardiographic tracings

TABLE I
Causes of Electrocardiographic Changes

1. Opening of chest
2. Pericardial incision
3. Ventricular manipulation
4. Coronary artery dissection
5. Insertion of atrial cannulae

TABLE II
Electrocardiographic Changes

1. Ventricular ectopic beats
2. Ventricular tachycardia and fibrillation
3. Flattening and disappearance of P waves
4. Atrioventricular dissociation
5. Flattening of T waves

which never returned to normal for the remainder of the procedure. In all the other patients, the changes noted were transient, required no therapy and their occurrence or frequency did not seem related to prognosis.

In poor risk patients, particularly those with severe pulmonary hypertension, aberrations were increased. Comparison of effects of ether and cyclopropane revealed no significant difference. On the other hand, restoration of good oxygenation and ventilation, cessation of cardiac manipulation and deepening of the anesthetic level frequently had a salutary effect.

When perfusion was discontinued, elevation in the ST segment was noted in eight patients, possibly indicating some myocardial hypoxia during the pump procedure. In most patients, the electrocardiographic tracing improved during closure of the chest and the immediate postoperative period.

Dr. Linde and his co-workers were interested in the relation of electrocardiographic changes to prognosis. The occurrence of sinus tachycardia, ventricular premature contractions, atrioventricular block and ventricular fibrillation during perfusion was not related to prognosis. They believe that the continuous monitoring of the electrocardiographic tracing by a cardiologist prevents the association of these abnormalities with a poor prognosis. At the first sign of difficulty, the surgeon was notified and appropriately altered the offending stimulus. Perhaps if the electrocardiogram had not been so monitored, these abnormalities would have been associated with a much poorer outcome.

During the procedure, impending difficulty could often be predicted when the electrocardiogram showed widening of the QRS complex or severe elevation or depression of the RS-T segment. The best hint of a good prognosis was the immediate return of the preoperative cardiographic pattern on cessation of perfusion.

Cardiac Resuscitation

Edited by PALUEL J. FLAGG, M.D., F.A.C.C.*

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The Treatment of Ventricular Fibrillation

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THE SUCCESSFUL clinical treatment of ventricular fibrillation became a reality a little more than a decade ago.[1] Up until then this serious arrhythmia was complacently accepted as incompatible with life. Considerable progress in treating ventricular fibrillation has now been made, particularly when it is recognized in patients in the operating room, but the reanimation of these people from clinical death is no doubt in its infancy.

Nothing can cause death as rapidly as ventricular fibrillation. There is an immediate fall of blood pressure to zero. Unconsciousness follows in a matter of ten to thirty seconds. The upper centers of the brain will be irreversibly damaged if deprived of oxygenated blood for more than three to four minutes under ordinary environmental conditions. During these precious minutes the patient is in a state of "clinical death" which can often be reversed, provided the proper resuscitation technic is undertaken. Death is final and irreversible.

The death factor in some instances can actually be small and reversible. One does not have to be struck by a locomotive or blown to bits by a bomb in order to have death overtake him. The precipitating factor can amount to a minor sudden physiological breakdown, the magnitude of which in certain circumstances is sufficient to produce cessation of the heart beat with consequent fatal deterioration of the cerebral cortex. Our serious attention must be directed toward the prevention of anoxia in those tissues of the body most sensitive to anoxia—the brain. We must never lose sight of this primary consideration.

COMMON CAUSES OF VENTRICULAR FIBRILLATION

Experience now indicates that cardiac resuscitation can be successful in certain cases of sudden clinical death outside of the operating room,[2] and possibly extramurally. For example, a reasonable attempt of resuscitation is feasible for those persons facing impending death from acute coronary insufficiency if the victim "dies" in the hospital.

It is the medical consensus that the majority of patients who die suddenly of acute coronary insufficiency undergo terminal ventricular fibrillation. However, this is only an academic question. According to Yater and Beck, many of these hearts show minimal or no myocardial damage and may under proper circumstances beat again if given a second chance, as a great many have relatively good myocardium. Any significant reduction of inflow of oxygenated blood through an artery to an isolated area (island) of the heart may disturb that area's metabolism, causing a cellular ionization change across its membrane which is electronically unstable and is recordable. This electrochemical instability may be sufficient to excite ventricular fibrillation. This statement obviously is an oversimplification of a complex reaction.

The particular location of this island may also be a factor, as Hooker[3] believed that the apical region is the most irritable portion of the heart and its threshold of fibrillation the least.

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Three similar instances of clinical death from ventricular fibrillation occurred within four months in a Cleveland Hospital* in 1959. Each arrived in the emergency ward of this hospital with severe anginal pain. Shortly thereafter in each instance, during the recording of an electrocardiogram, ventricular fibrillation, as well as other signs of clinical death were observed. The same physician successfully resuscitated each of these patients in the emergency ward, and they left the hospital in relatively good condition with no evidence of cortical damage. Will the future consider such recordings as commonplace?

Some of the other ordinary causes of ventricular fibrillation are: (1) electrocution from weak currents reaching the heart (75 to 200 m.a.) such as residential current; strong electrical currents do not cause fibrillation; (2) overdosages of exogenous or endogenous epinephrine; (3) certain anesthetic agents such as the chloroform-cyclopropane group or this group in combination with epinephrine; (4) hypothermic conditions and drowning in fresh water; and (5) occasionally electroconvulsive therapy and so-called electronic sleep induction machines.

Treatment

For the successful treatment of ventricular fibrillation it is mandatory to have trained personnel and certain equipment immediately available. It is important to know the things not to do, as well as the things to do. Each step must follow in an orderly chronological sequence, otherwise the omission or erroneous commission of some so-called minor act may be incredibly responsible for failure. In this extraordinary emergency there is no place for error and no time for consultation or gluteal cerebration.

The resuscitation procedure is divided into two separate and distinct steps. The two components are (1) re-establishment of the "oxygen system," or respiratory resuscitation†; (2) restoration of the heart beat. The re-establishment of the oxygen system is the emergency act. Once the first step is achieved, the crisis is over. Oxygenated blood is being delivered to the brain, and the heart beat can then be restored without special reference to time. Further help and aid can then safely be summoned.

A definite step-by-step preconceived plan must be put into effect. Most failures are attributed to the so-called resuscitation time limitation of three to four minutes and incompatible cardiac disease.

Respiratory Resuscitation: Oxygen must be delivered into the lungs by the means available at the time. The anesthetist must be able to do this as the surgeon has too many other obligations at this moment. The best and surest method of delivering oxygen into the lungs is to introduce a properly fitting intratracheal tube which is attached to a rubber bag filled with 100 per cent oxygen. At the same time the surgeon grasps a knife and boldly makes a large intercostal incision from the sternum to the underlying sheet. Time is not taken to count the interspaces, but a suitable space immediately below the left breast is preferred.

Cardiac Massage: The right hand, gloved or ungloved, is thrust between the ribs and the lung judiciously pushed aside. The hand is placed beneath the heart and the intact pericardium and then the heart with its intact pericardium is squeezed upwards against the sternum, thus pumping oxygenated blood to the brain and vital organs. At this moment the crisis is over, the oxygen system has been re-established. The heart has again become a functioning hemodynamic pump and its efficiency as such will depend a great deal upon the operator's technic and ability.

If the person delivering the oxygen to the lungs is doing a good job, it will be necessary to stop momentarily in order to enlarge the incision as the wrist will feel strangulated within a short time. This is done by cutting the costochondral junctions of the adjacent ribs. After resuming massage again, a short time is taken for the placement of a rib spreader and for opening the pericardium. It is assumed the heart is found in a fibrillating state. Although there is a fine movement of the myocardium, there is no ejection or propulsion of blood.

Electrical Defibrillation: Massage‡ is resumed again, and when the myocardium is pink the electrodes of a defibrillating machine are placed firmly on each ventricle and a shock applied. The electrocardio graph must be disconnected at this time. It is best to squeeze its walls together with moist electrodes. This will tend to empty its chambers. It is hoped that an initial shock will return the heart to a coordinated beat. However, if it does not, repetition of this procedure is carried out a good many times. As a last

* Personal communication from Ralph Smith, M.D.

† Flagg, P. L. Doctrine of Hypoxia. *Am. J. Cardiol.*, 2: 513, 1958.

‡ For details the reader is referred to: R. M. Hosler, M.D. Manual on Cardiac Resuscitation, 2nd ed. Springfield, Illinois, 1958. Charles C Thomas.

resort, 3 or 4 cc. of 1 per cent procaine may be injected within the chamber of the right ventricle followed by effective massage and additional electrical shocks. If success does not occur and the myocardium has become flabby, 2 cc. of 1 to 10,000 dilution of Adrenalin® solution is injected into the chamber even in the face of ventricular fibrillation.

The length of time diligently devoted to this life-saving procedure depends upon the one in charge. Somewhere along the line the oxygen system must be given back to the victim. It is hoped that he can take it over, otherwise absolute death will supervene. Persistence will often lead to success.

As the cardiorespiratory system again begins to function satisfactorily it is suggested that atropine sulfate gr. $^1/_{150}$ and 4 cc. of cedilanid-D be given intravenously. Experience seems to indicate that this is advantageous.

Closed-Chest Defibrillation: The most serious obstacle to overcome in present-day resuscitation is the necessity of opening the chest. Experiments now indicate that closed-chest resuscitation[4] may become a practical reality. Accomplishment of external defibrillation has been done for many years. However it has not proved practical in restoring a circulation much beyond 45 to 55 seconds.[5,6] Failure is not from inability to place the heart in defibrillation, but from inability to restore a blood pressure compatible with life.

The author[4] has carried out closed-chest defibrillation experiments in dogs whose hearts had been in state of ventricular fibrillation for more than 60 seconds. The supplemental procedure used to restore the circulation after external defibrillation had been accomplished, was the intra-arterial perfusion of epinephrine solution and dextrose through a large bore needle under 200 to 250 mm. Hg pressure. This augmentative procedure resulted in the circulation being restored after it had been arrested for 2.25 to 3 minutes without need for opening the chest and direct cardiac massage. This type of procedure has more appeal to medical men and internists.

It is obvious that such a procedure cannot be carried out haphazardly in a medical ward. Previous preparation for such a procedure should be made. Otherwise, a frantic, inefficient atmosphere may prevail during the emergency. Intra-arterial infusion or transfusion in some hands can require more training and technic than thoracotomy.

Present-day practical consideration of the two augmentative procedures, thoracotomy with massage and intra-arterial pressurized infusions, indicates the former is still the method of choice and the more reliable. There must be persistence in the search for means of supplying oxygenated blood to the coronary system under a minimum pressure of 40 mm. Hg. This is the stimulus par excellence for a quiescent heart. Individual cardiac muscle cells soon lose their inherent characteristic of excitability and their ability to respond to a stimulus after thirty seconds of anoxia.

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Workmen's Compensation for the Cardiac

Relation of Recurring Myocardial Infarction to a Previous Infarct

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WE WILL discuss in this paper the fifth question the Morland Commission submitted to cardiologists and internists with reference to causal relationship of strain and cardiac disability.[1] The question reads as follows: "*Assume that a workman suffered a myocardial infarction, and that it was a compensable injury under the Workmen's Compensation Law. He recovered and was discharged as cured, and then returned to work. A year or more later, not during the course of his employment and not due to any physical exertion, he has another attack of coronary occlusion, with myocardial infarction. In your opinion, would the second attack be causally related to the first?*"

There were 381 replies. Of these 51 or 13.3 per cent said yes, possible or probable and 330 or 86.7 per cent said specifically no or implied no in their answer.

It appears to me that the statement "he recovered and was discharged as cured" needs elucidation Do we mean by the term "cured" that the patient recovered functionally well enough to resume his normal activity or that the anatomic structural cardiac damage caused by the infarction has entirely cleared up? The former may possibly occur in many cases. The latter, however, is hardly to be expected except perhaps in those cases in which the myocardial infarction was trivial and was fully absorbed in the acute phase, leaving little scarification. In the majority of cases the infarction is large enough to leave considerable gross scarification, and the heart may thus be considered to be structurally damaged in the area of the infarct, although the functional capacity of the heart may be within normal limits for ordinary activities.

Importance of Location of Second Infarction: To properly answer the question that the commission submitted we must individualize each case. Let us assume that the given individual considered "cured" remains asymptomatic and is able to carry on his normal activities, even though there may be some degree of demonstrable anatomic damage left. These activities have been continued for one or more years uninterruptedly and without any discomfort. At the end of that time he suddenly has another attack of myocardial infarction. The factor to be determined as to causal relationship of the second attack and the previous involvement is the location of the second infarction. If the second infarction is in an area remote from the previous infarct, it could not be logically considered causally related to the original infarct. It should merely be considered to be caused by a fresh independent coronary occlusion in another coronary artery which was the seat of progressive coronary atheromatosis. If, however, the second infarction occurred in the same area of the previous infarct or close to it, we may assume that the accentuated pathologic changes occurring in the coronary artery during the previous partial or complete occlusion which caused the first

* Chairman, Workmen's Compensation Committee, American College of Cardiology.

infarction was a predisposing factor to a recurring coronary occlusion and myocardial infarction. We can easily visualize how an occlusive process in one of the coronary arteries may predispose that artery to greater distention and strain above the area of occlusion. The collateral circulation that may develop in the area may not be sufficient to compensate for the increased damage in that vessel.

Effect of Initial Coronary Closure on Remaining Coronary Arteries: The theory that closure of one of the coronary arteries causing destruction of a portion of the heart muscle throws a greater burden on the other coronary vessels and on the rest of the myocardium may hold true in some cases but certainly not in all. It is a common experience to see people who have had an acute myocardial infarction go on at times for many years without any gross cardiac enlargement, cardiac failure or the anginal syndrome. If the pathologic changes resulting from an infarction would throw a greater burden on the remaining coronary arteries or on the rest of the myocardium, we would expect to find some subjective disturbances and objective cardiac enlargement gradually developing following the first insult.

It is also a common observation, however, that in some instances a person was symptom-free previous to the development of an infarct and following the infarct a greater or lesser degree of angina or dyspnea on exertion develops. If these patients are followed up for a prolonged period, some progressive cardiac enlargement is noted to develop. These patients usually have marked residual damage at the site of the original infarction. In many others arterial hypertension may be present. In still others atherosclerosis of all the coronary arteries might have been marked and rapidly progressive, although it was asymptomatic before the first acute myocardial infarction. It is reasonable to assume in such cases that the coronary occlusion and myocardial infarction have thrown a greater burden on the rest of the diseased coronary arterial system, predisposing it to recurring coronary occlusion and myorcardial infarction or to heart failure.

It is thus seen that to logically answer the question posed in this paper, each individual case must be carefully evaluated and studied. The variations are so marked as to make it impossible to give a yes or no answer in all such cases.

Reference

1. Sigler, L. H. Results of a questionnaire on relationship of exertion to myocardial infarction. *Am. J. Cardiol.*, 2: 781, 1958.

The Query Corner

READERS are invited to submit queries on all aspects of cardiovascular diseases. Insofar as possible these will be answered in this column by competent authorities. The replies will not necessarily represent the opinions of the American College of Cardiology, the JOURNAL or any medical organization or group, unless stated. Anonymous communications and queries on postcards will not be answered. Every letter must contain the writer's name and address, but these will not be published.

Electrocardiogram in Single Ventricle

Query: (1) Why is the duration of QRS normal in patients with cor triloculare biatrium despite the absence of the interventricular septum? (2) What determines the axis deviation of the electrocardiogram in patients with cor triloculare biatrium? Although most patients show right axis deviation, at least two patients have been reported to show left axis deviation.

Answer: The single ventricle cannot be considered a special entity. The important aspect is the other malformations which are associated with a single ventricular cavity. In the postmortem material at the Institute of Cardiology in Mexico City we have found the description of four cases which we have considered to fall into the group of the single ventricle.

CASE 1. The first case corresponds to a single ventricle with transposition of the great vessels with orificial and infundibular stenosis of the pulmonary artery. There is no interventricular septum. Instead there are dorsal and ventral muscular rudiments of the interventricular septum. Both pulmonary artery and aorta emerge from the right side of the heart, lateral to an imaginary line drawn from the ventral and dorsal rudiments. The free right ventricular wall and crista supraventricularis were markedly hypertrophied.

Electrocardiographic findings: AQRS points toward the right (plus 180 degrees in the frontal plane) and towards the front (tall R waves in V_1 and V_2, deep S waves in V_5 and V_6). QRS duration is 0.08 second.

CASE 2. Single ventricle without transportation of the great vessels with aortic pulmonary disposition of the Fallot type; pulmonary stenosis and dextraposition of the aorta. The right free ventricular wall is hypertrophied with marked enlargement of the left portion of the heart. There is a small rudiment of the ventral portion of the septum forming part of a large hypertrophied crista supraventricularis.

Electrocardiographic findings: AQRS points downward, slightly to the left and back (plus 90 degrees in the frontal plane). Electrically, neither ventricle predominates, which is in accordance with the anatomic findings, even though the electrocardiogram suggests enlargement of both cavities. QRS duration is 0.08 second.

CASE 3. Single ventricle with rudimentary left ventricle where a stenotic pulmonary artery emerges; bilocular heart and levocardia.

Electrocardiographic findings: AQRS points to the right (plus 130 degrees in the frontal plane) and to the front (large RS complexes from V_1 through V_4, also r and S in V_5 and V_6), findings in accord with the rudimentary left ventricle. QRS duration is 0.06 second.

CASE 4. Single ventricle with common trunk. Cor biloculare and single mitral tricuspid orifice with a small ventral rudiment of the septum. Marked hypertrophy of the right ventricle* mainly near the crista supraventricularis.

Electrocardiographic findings: AQRS points upward (minus 135 degrees in the frontal plane) and to the right. The unipolar morphology of the right ventricle is recorded from V_1 through V_6 which is in accordance with the anatomic findings of marked right ventricular hypertrophy of the crista supraventricularis. QRS duration is 0.06 second.

* When we mention right ventricle, we refer to the right position of the single ventricle.

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Digitalis Toxicity in Uremia

Query: How would you treat an ectopic arrhythmia induced by digitalis toxicity in a patient with uremia?

Answer: The administration of digitalis should be stopped in all instances and occasionally this may be all that is necessary, depending

upon the type of digitalis that was being used and the seriousness of the ectopic rhythm.

Uremia may be associated with a low, normal or elevated serum potassium concentration and may reflect chronic or acute renal insufficiency, with or without oliguria. If the serum potassium is low or normal and there is no oliguria, potassium salts may be administered slowly, intravenously, with continuous electrocardiographic monitoring: 10 mEq. of potassium chloride per 100 cc. of isotonic or hypertonic (calories) glucose should be given. If the serum potassium is elevated, close clinical and electrocardiographic observation may be all that is necessary.

If oliguria is present, potassium therapy should be withheld for as long as possible, i.e., until A-V dissociation progresses to ventricular tachycardia. Should this occur extreme caution in the administration of potassium is mandatory and only enough potassium should be given to return the ectopic rhythm to a less serious electrocardiographic manifestation of digitalis intoxication.

If the digitalis-induced ectopic rhythm is observed during the oliguric phase of acute renal failure, potassium should not be given until a progression in the arrhythmia is observed. When the patient enters the diuretic phase, large quantities of intravenous potassium replacement therapy may be necessary to prevent sudden death from digitalis intoxication; daily potassium losses in the urine in this recovery phase are great.

Magnesium levels often parallel potassium levels in renal failure, but occasionally small amounts of intravenous magnesium salts may improve digitalis-induced arrhythmias. There appears to be little place for sodium versenate (EDTA) in most instances of uremia, particularly when there is coexistent hypocalcemia. The use of quinidine and procaine amide in treating uncomplicated digitalis intoxication remains controversial, and these agents should be avoided in the presence of renal insufficiency.

If the ectopic rhythm proved to be complete A-V heart block the use of Isuprel®, particularly if the serum potassium is normal or only slightly elevated, may be gratifying. The judicious administration of small quantities of molar sodium lactate and/or hypertonic glucose (with or without supplemental regular insulin) may be life-saving in the presence of an elevated serum potassium level.

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Recurrent Ventricular Tachycardia

Query: A fifty-year old woman without apparent heart disease has had recurrent and disabling episodes of ventricular tachycardia for at least ten years, despite the prophylactic use of the presently available drugs, including quinidine, procaine amide and digitalis. Have you any other recommendations for preventive therapy?

Answer: There are no sure preventive measures at this writing. However, reserpine alone or in combination with the use of long acting quinidine (Dura-tab Quinidine Gluconate 0.3 gm. [5 gr.] every eight or twelve hours) merits a trial. Reserpine is recommended because of its known bradycardic effects (ALBANO, T. and MOTTA, R. *Minerva med.*, 49: 3904–3909, 1958) and because of its observed favorable effects in other arrhythmias (FONTANINI, F., RIVI, A. and SIGNORELLI, S. *Minerva med.*, 49: 3815–3822, 1958). This action of reserpine is believed to be mediated through the release of norepinephrine from the myocardium.

The suggested dose: 0.1 mg. every eight hours for one week, 0.1 mg. every twelve hours for the second week and 0.1 mg. once daily thereafter.

If the patient can be kept under close observation and no side effects develop, larger doses, e.g., twice these suggested amounts may be tried.

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